Lecture – Autumn 2016

INTRODUCTION to PSYCHOPHARMACOLOGY

Antipsycotics

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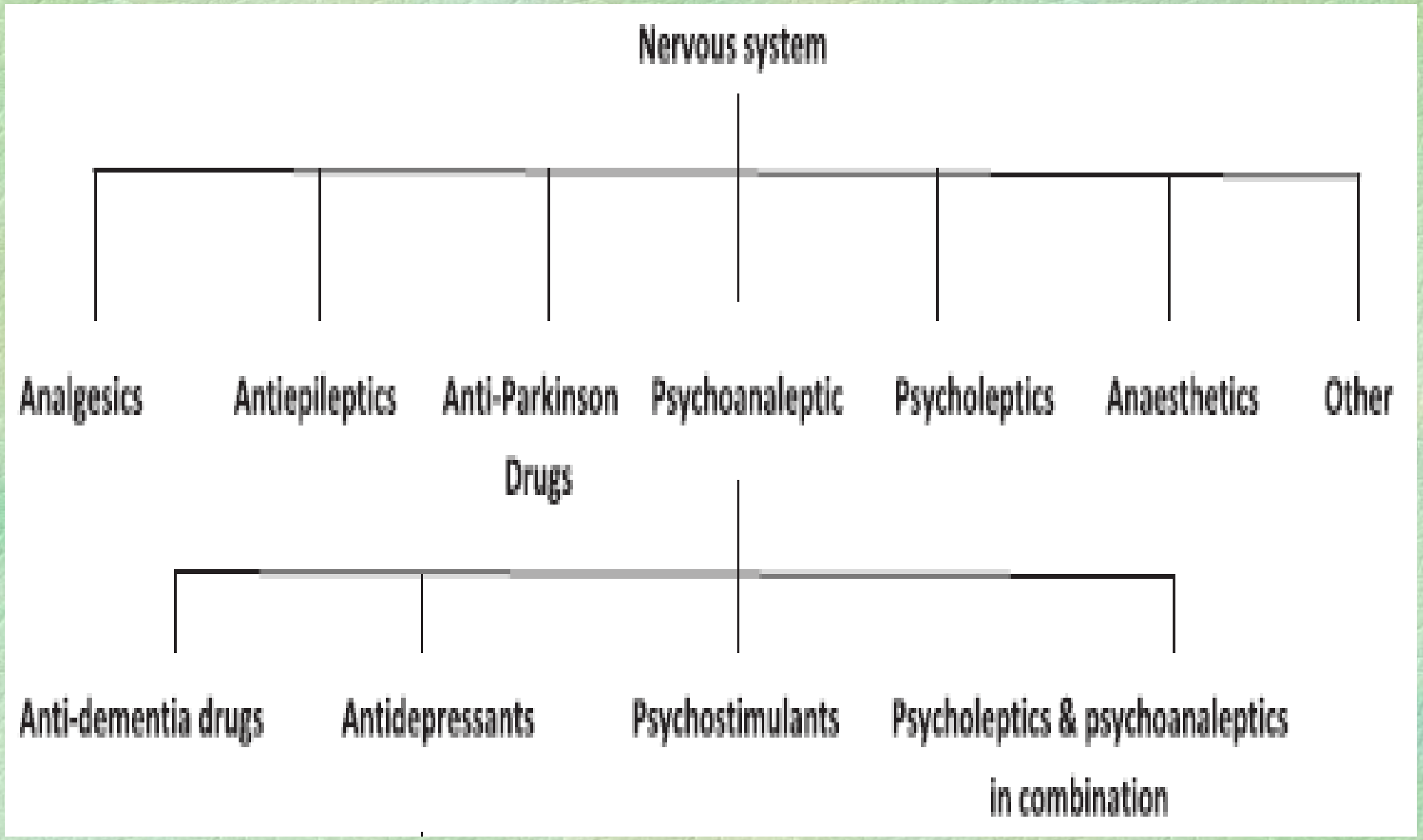
WHO nomenclature of NEUROPSYCHOTROPICS



ECNP (European College of Neuropsychopharmacology)
and
CINP (International College of Neuropsychopharmacology)

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NEW Neuroscience Based Nomenclature of Psychotropics

Generic drug name

Class – acording to pharmacological mechanism of action

Indication

Eeffectiveness and side effects

Neurobiological data (preclinical and clinical)

- **interactions with neurotransmitters**
- **physiology**
- **brain pathways**

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NEW NOMENCLATURE OF NEUROPSYCHOTROPICS in axis 1 – 5:

PROPOSED TEMPLATE FOR
A MULTI-AXIAL PSYCHOPHARMACOLOGICAL NOMENCLATURE

Axis 1 Class (primary pharmacological target)
Relevant mechanism

Axis 2 Family (primary neurotransmitter(s)
and relevant mechanism)

Axis 3 Neurobiological activities (Animal, Human)
Neurotransmitter effects
Brain circuits
Physiological

Axis 4 Efficacy and major side effects

Axis 5 Indication(s)

Table 8 vortioxetine. *Multi-axial psychopharmacological nomenclature for vortioxetine*

Axis 1	**Class** serotonin		
	Relevant mechanism: reuptake inhibitor, receptor antagonist and partial agonist		
Axis 2	**Family**		
	Multimodel drug: Serotonin reuptake inhibitor, 5-HT_3, 5-HT_7, 5-HT_{1D} receptor antagonist, 5-HT_{1A} and 1B receptor partial agonist		
Axis 3	**Neurobiological activity**		
		Animal	Human
	Neurotransmitter effects	Increases 5-HT NA, DA, and ACh in ventral hippocampus and prefrontal cortex Histamine in medial prefrontal cortex 5-HT in nucleus accumbens	Occupies SERT in raphe nucleus (PET)
	Brain circuits	Increases cortical neurotransmitter activity via disinhibition of the raphe nucleus and peripheral 5-HT receptors	
	Physiological		Suppresses REM sleep
Axis 4	**efficacy and major side effects**		
	Improves cognitive dysfunction in depression		
Axis 5	**approved indications**		
	Major depressive disorders		

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NEW NOMENCLATURE OF NEUROPSYCHOTROPICS in axis 1 – 5:

PROPOSED TEMPLATE FOR
A MULTI-AXIAL PSYCHOPHARMACOLOGICAL NOMENCLATURE

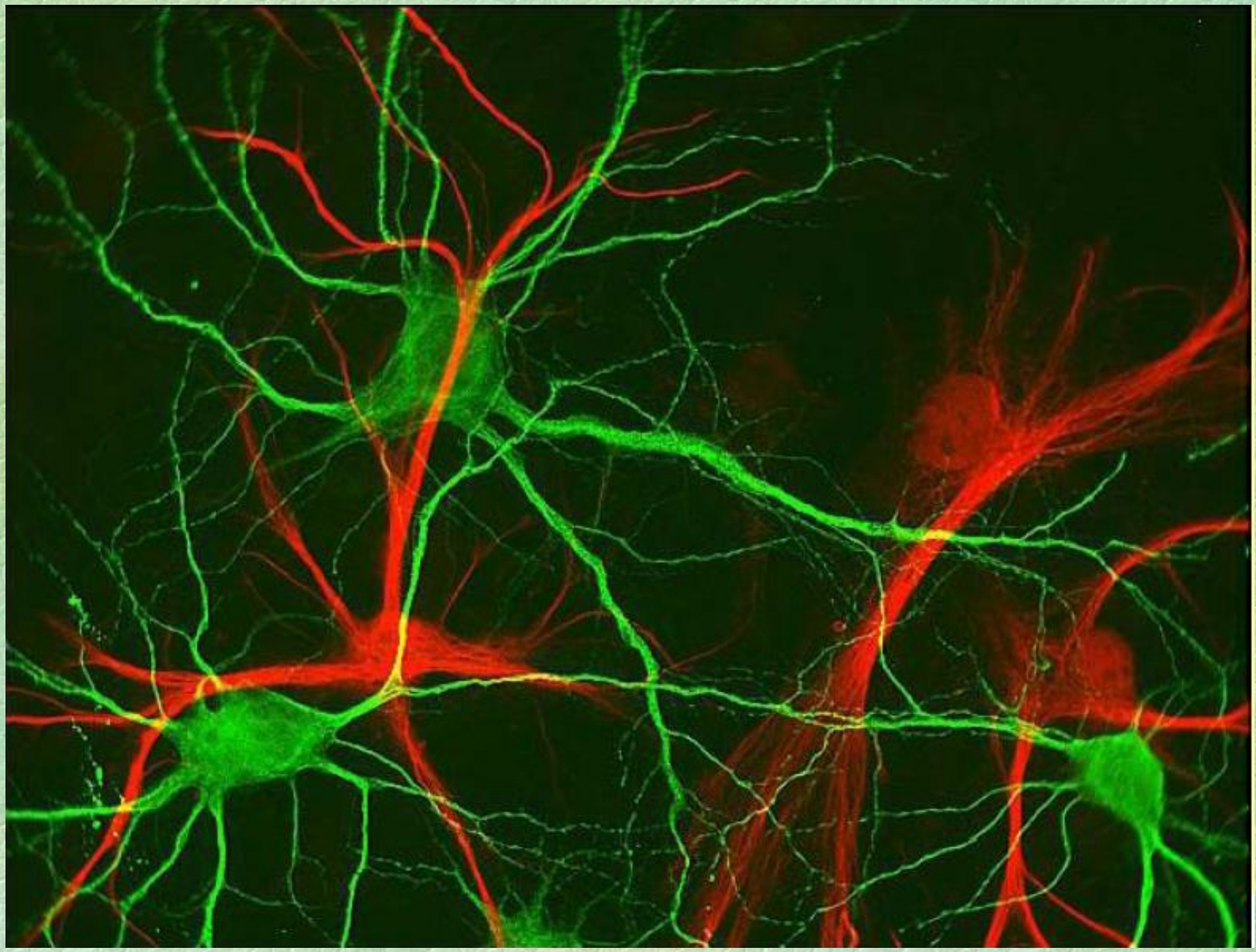
Axis 1 . . .

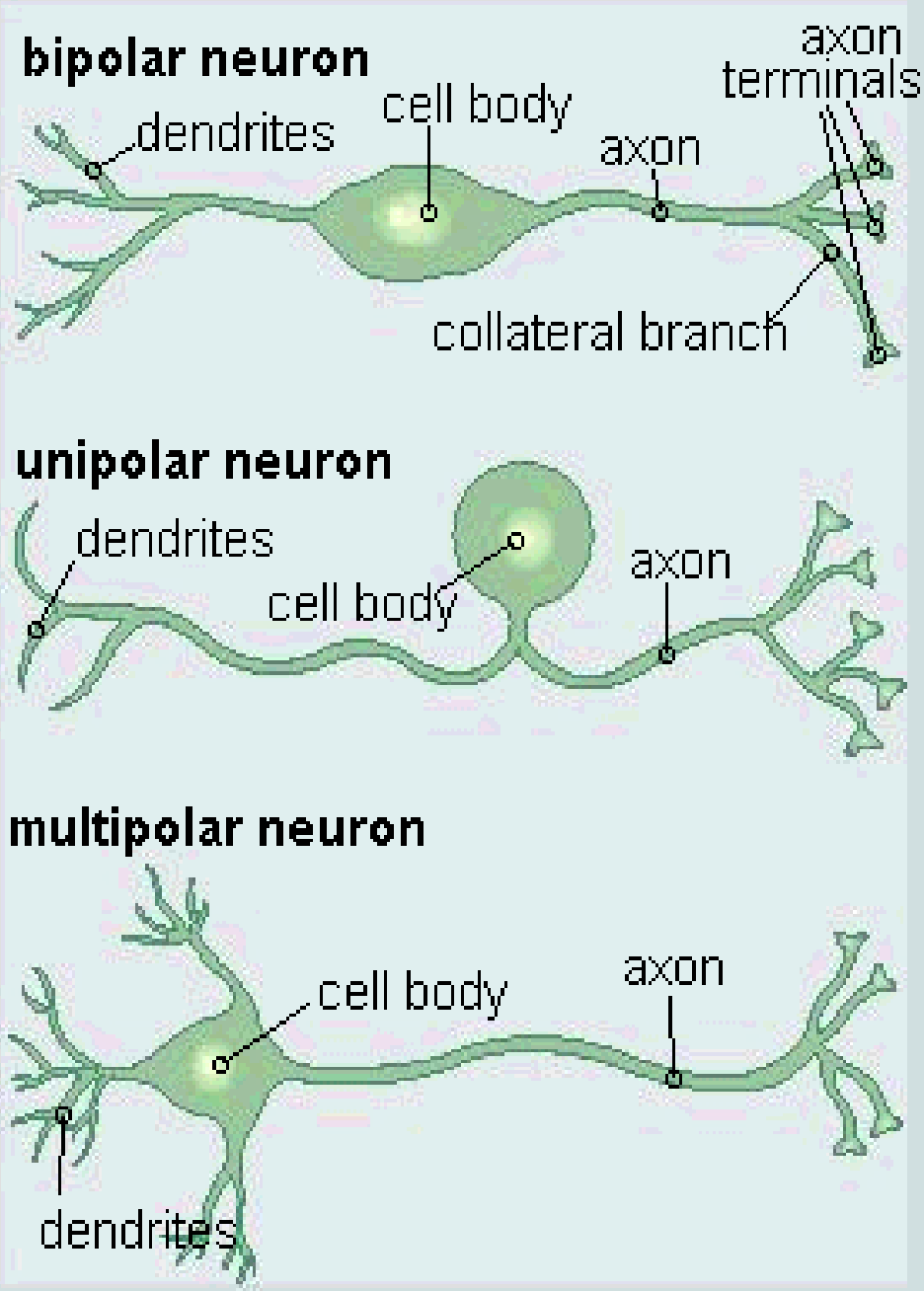
Axis 2 . . .

Axis 3 Neurobiological activities (Animal, Human)
- **Neurotransmitter effects**
- **Brain circuits**
- **Physiological**

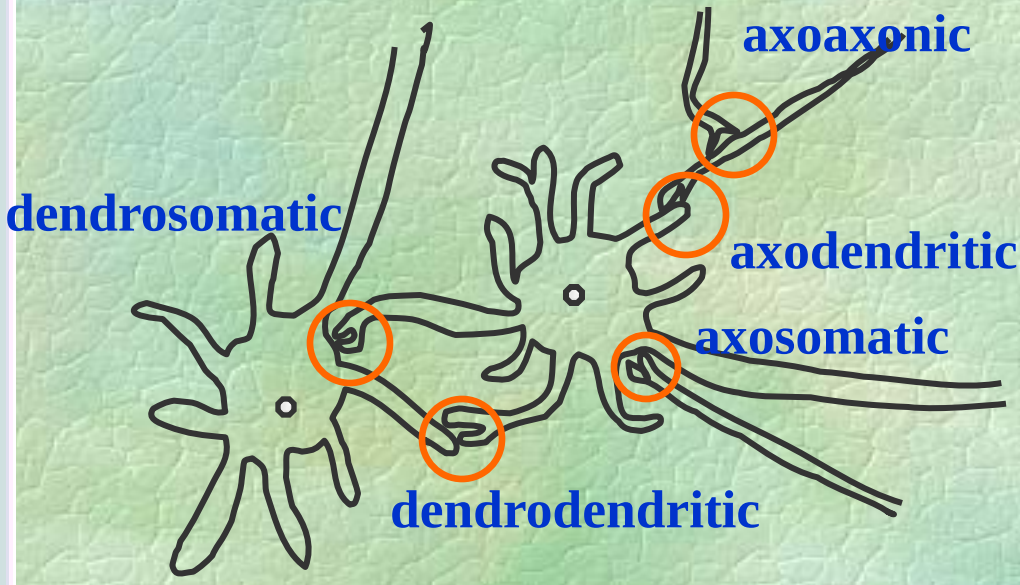
Axis 4 . . .

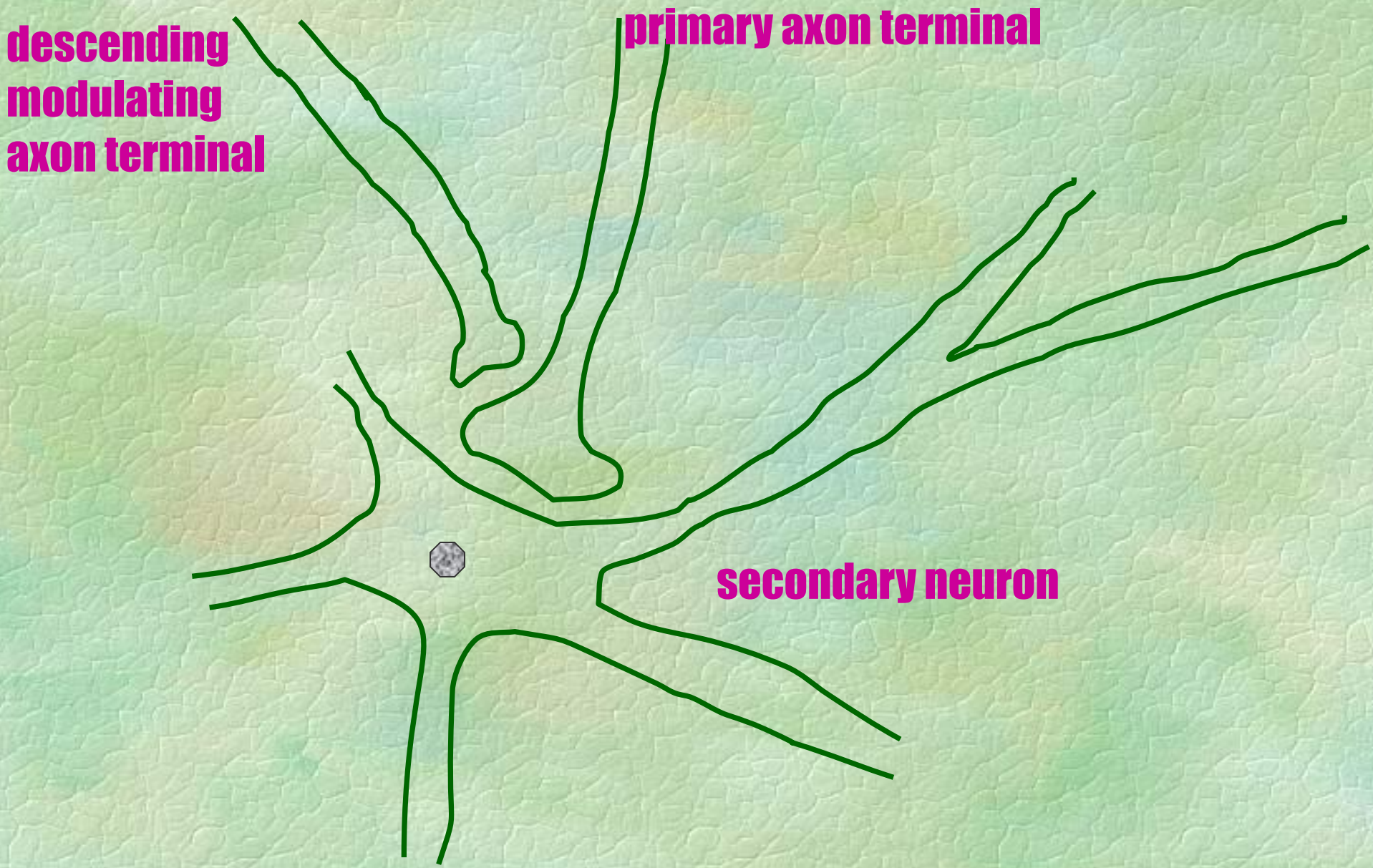
Axis 5 . . .



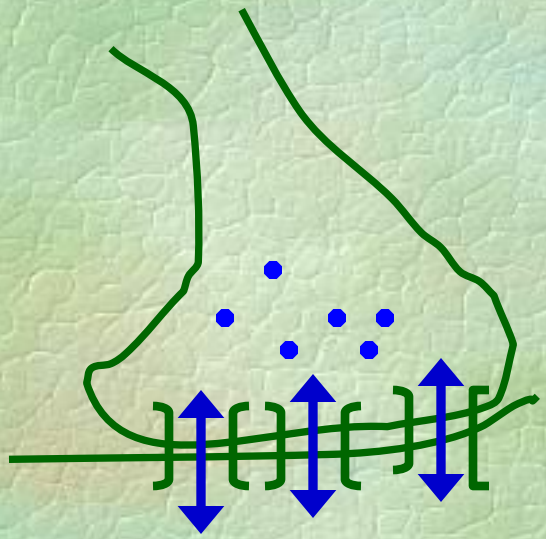


TYPES of SYNAPSES

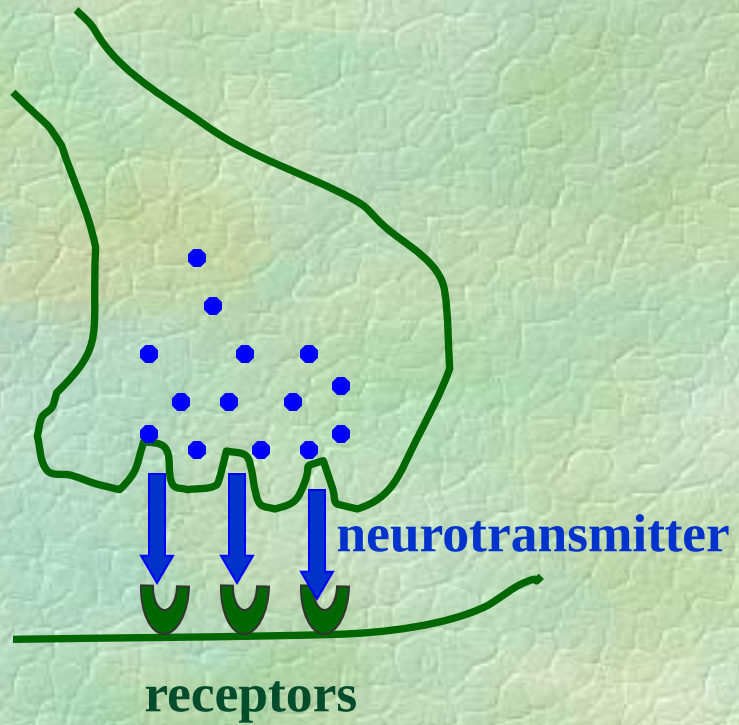



descending
modulating
axon terminal
primary axon terminal
secondary neuron

SYNAPSE



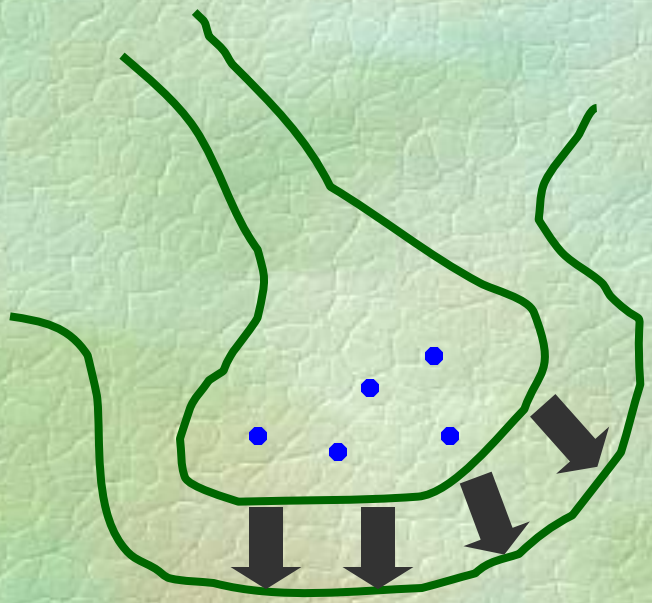
electrical
("gap junction")



chemical

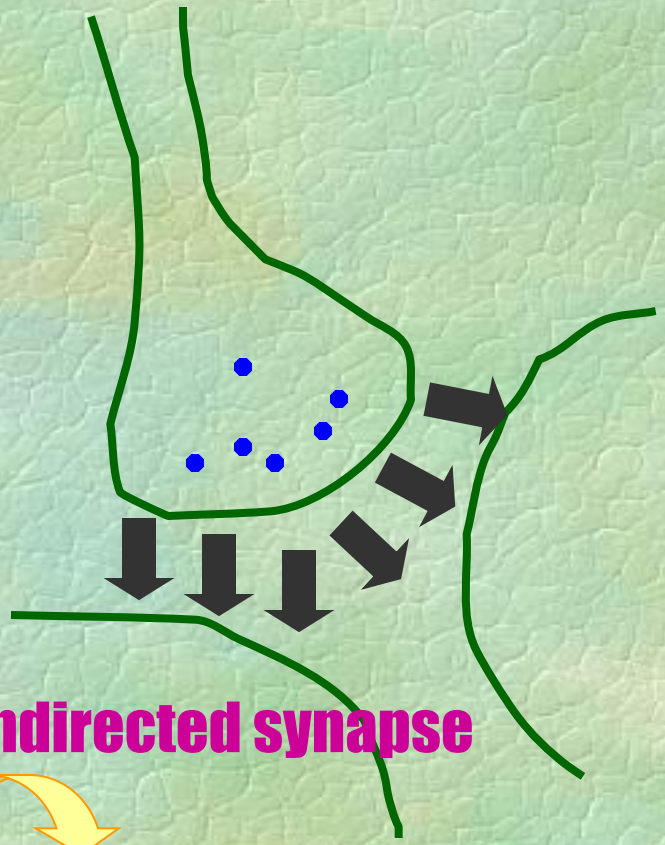
bidirectional passage of ions and
small molecules through channels

CHEMICAL SYNAPSES



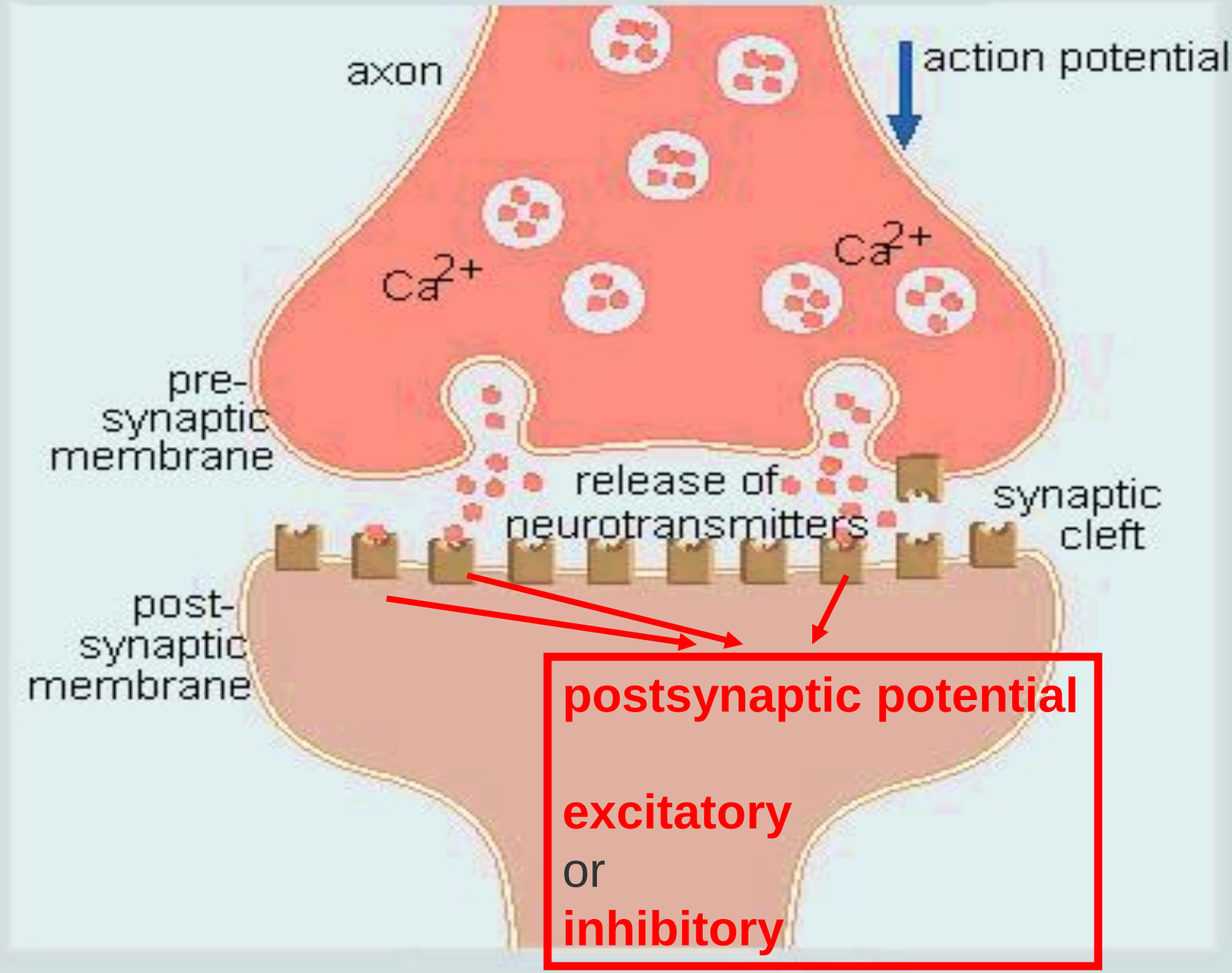
directed synapse

20 - 30 nm

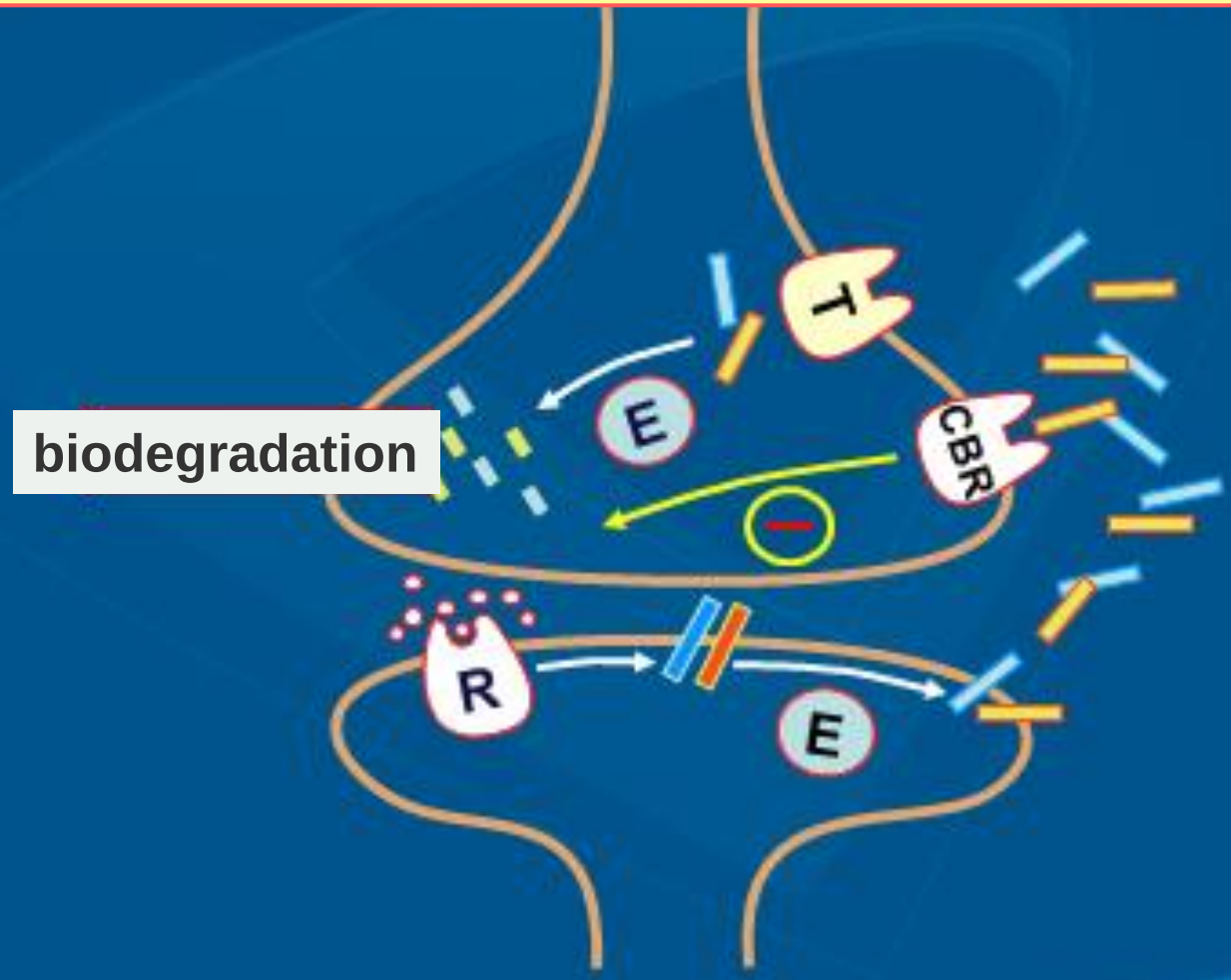


nondirected synapse

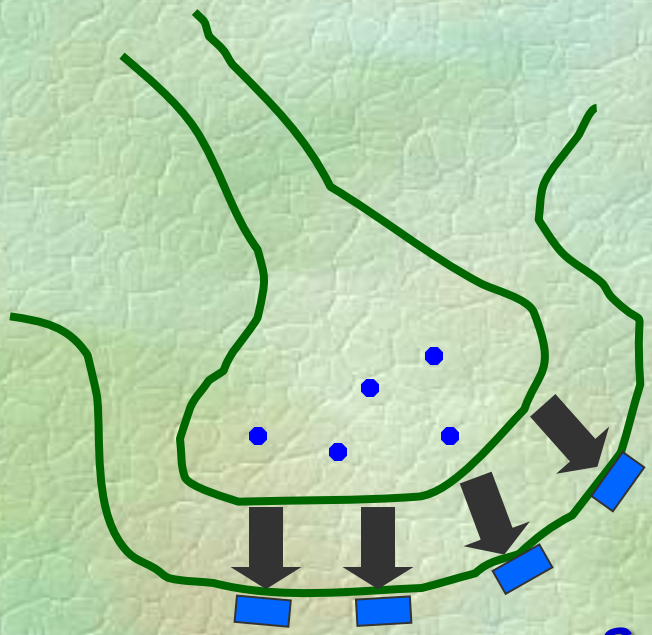
till 400 nm


axon
action potential
Ca^{2+}
Ca^{2+}
pre-
synaptic
membrane
release of
neurotransmitters
synaptic
cleft
post-
synaptic
membrane
postsynaptic potential
excitatory
or
inhibitory

“RETROGRADE NEUROTRANSMISSON“
e.g.: Synaptic functions of the endocannabinoid system

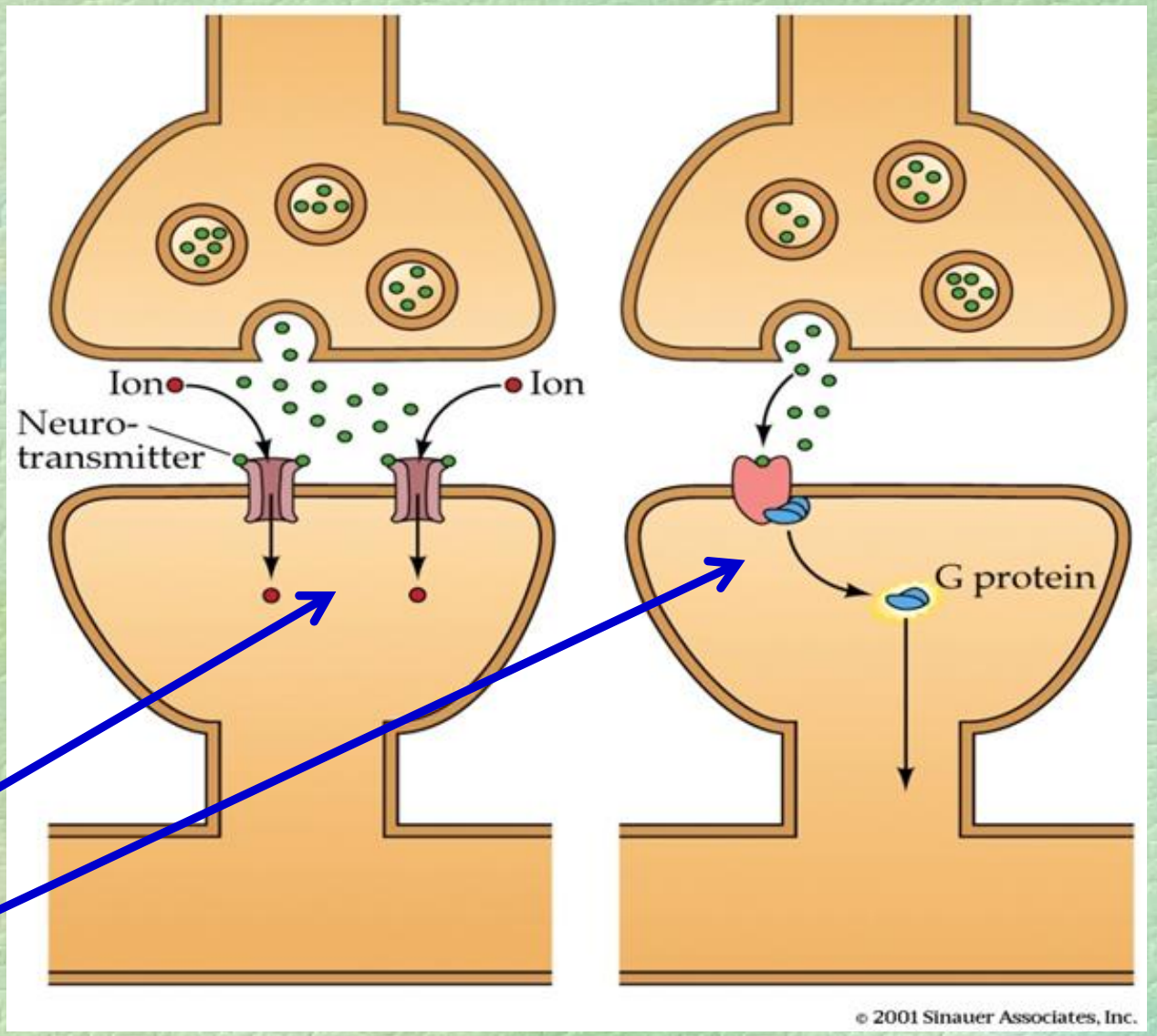


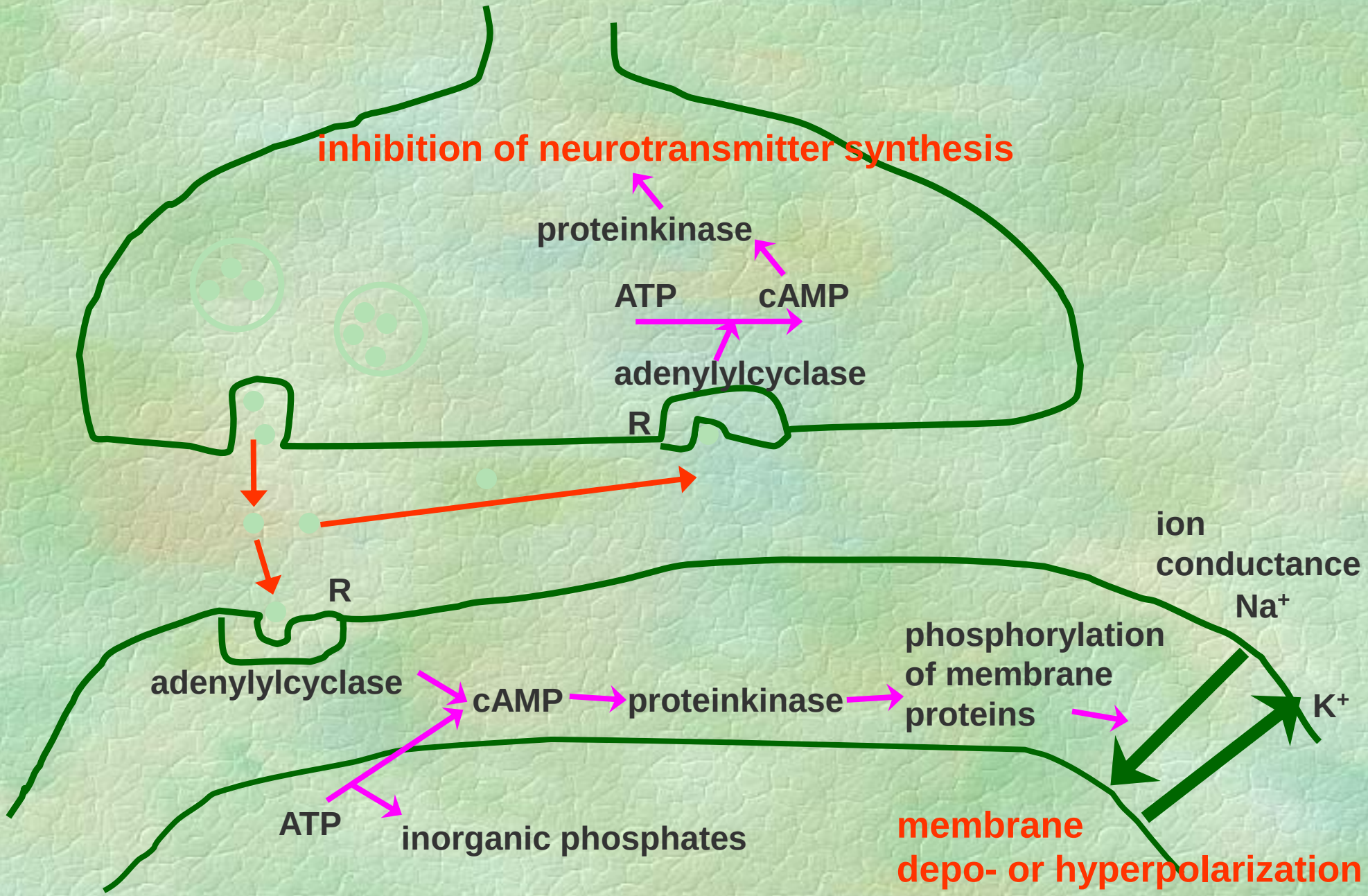
CHEMICAL SYNAPSE

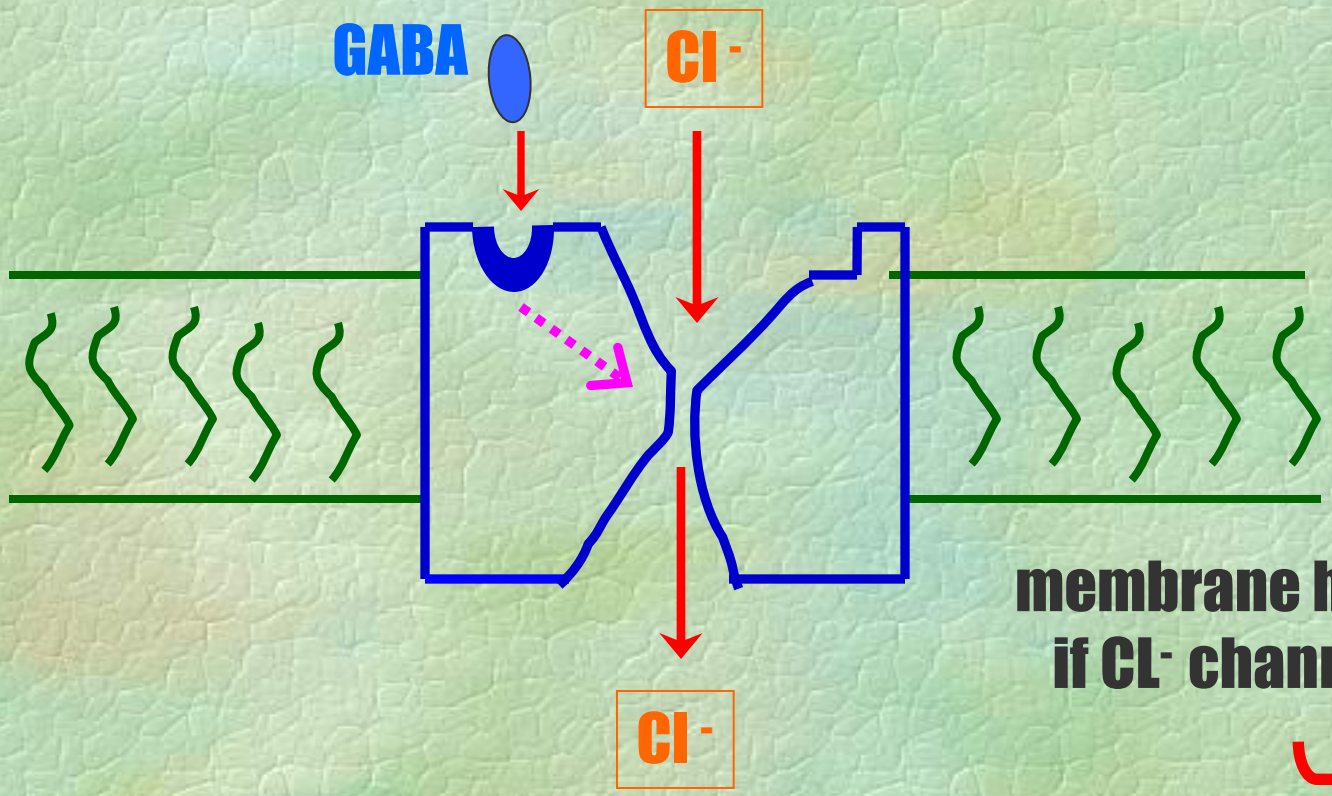


receptors

- ionotropic
- metabotropic (subtypes)



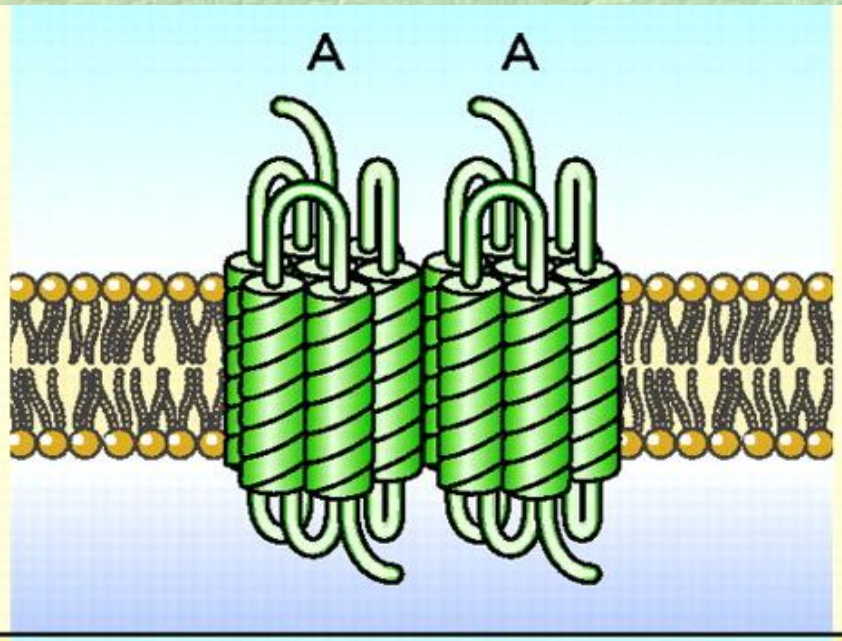

inhibition of neurotransmitter synthesis
proteinkinase
ATP
cAMP
adenylylcyclase
R
R
adenylylcyclase
cAMP
proteinkinase
phosphorylation of membrane proteins
ion conductance
Na+
K+
ATP
inorganic phosphates
membrane depo- or hyperpolarization



membrane hyperpolarization
if CL- channels are opened

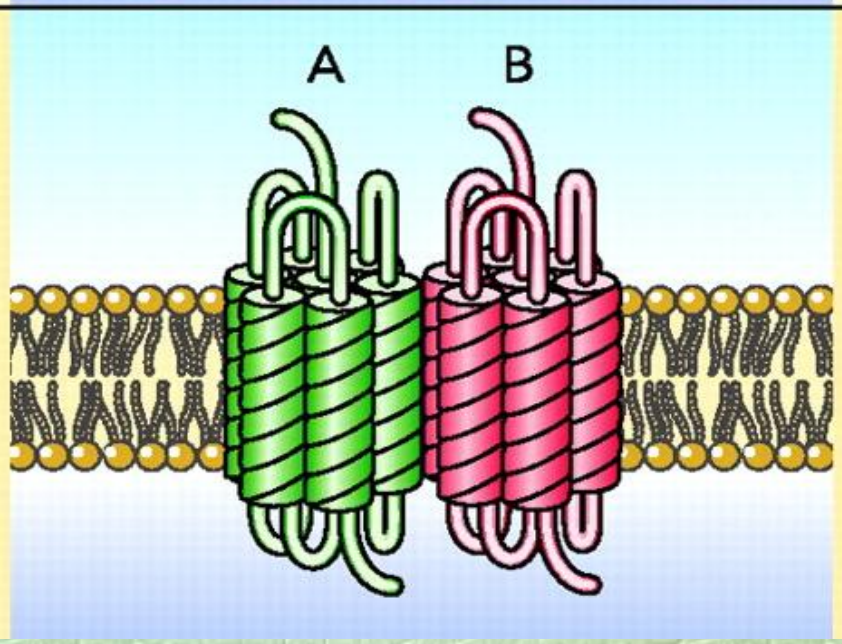
inhibiting influence
of GABA

Homodimers



One functional outcome possible

Heterodimers



Two functional outcomes possible

Differential degree of receptor activation determining A over B or B over A dominance

A>B B>A

Kjell Fuxe et al., Physiology, 2008, 23: 322-332

Kearn CS et al. **Concurrent stimulation of cannabinoid CB1 and dopamine D2 receptors enhances heterodimer formation: a mechanism for receptor cross-talk?**
Mol. Pharmacol. 2005;67(5):1697-704
.

Activity of heterodimers of MT a $5HT_{2C}$ receptors can influence SCN

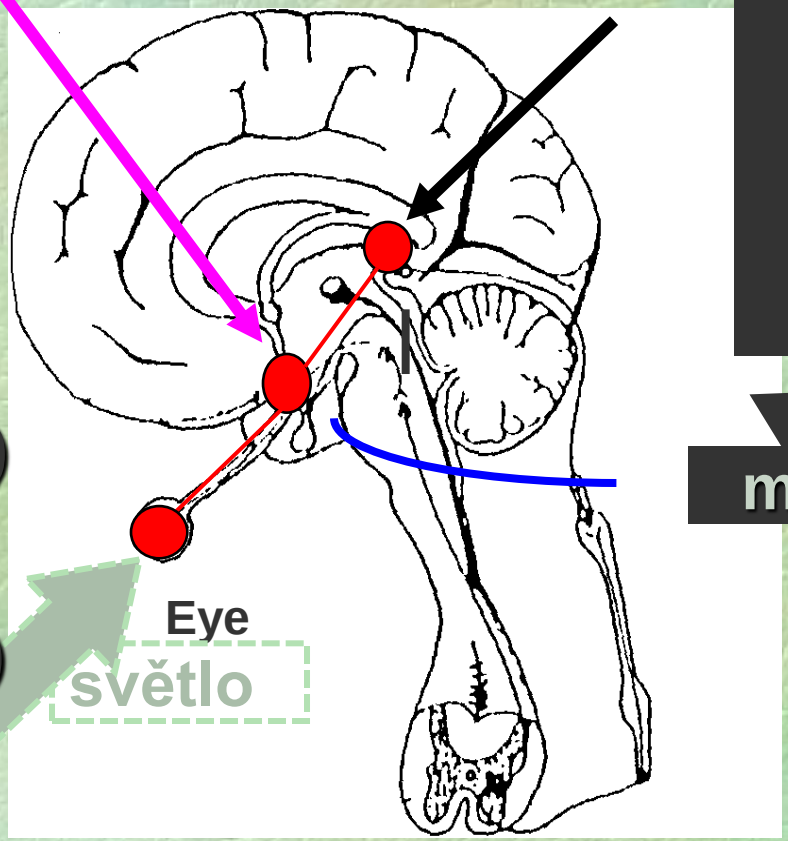
Suprachiasmatic Nuclei (SCN) = circadian clock

Agomelatin
(VALDOXAN, Servier)

agonist MT_1 (Mel_{1A})

agonist MT_2 (Mel_{1B})

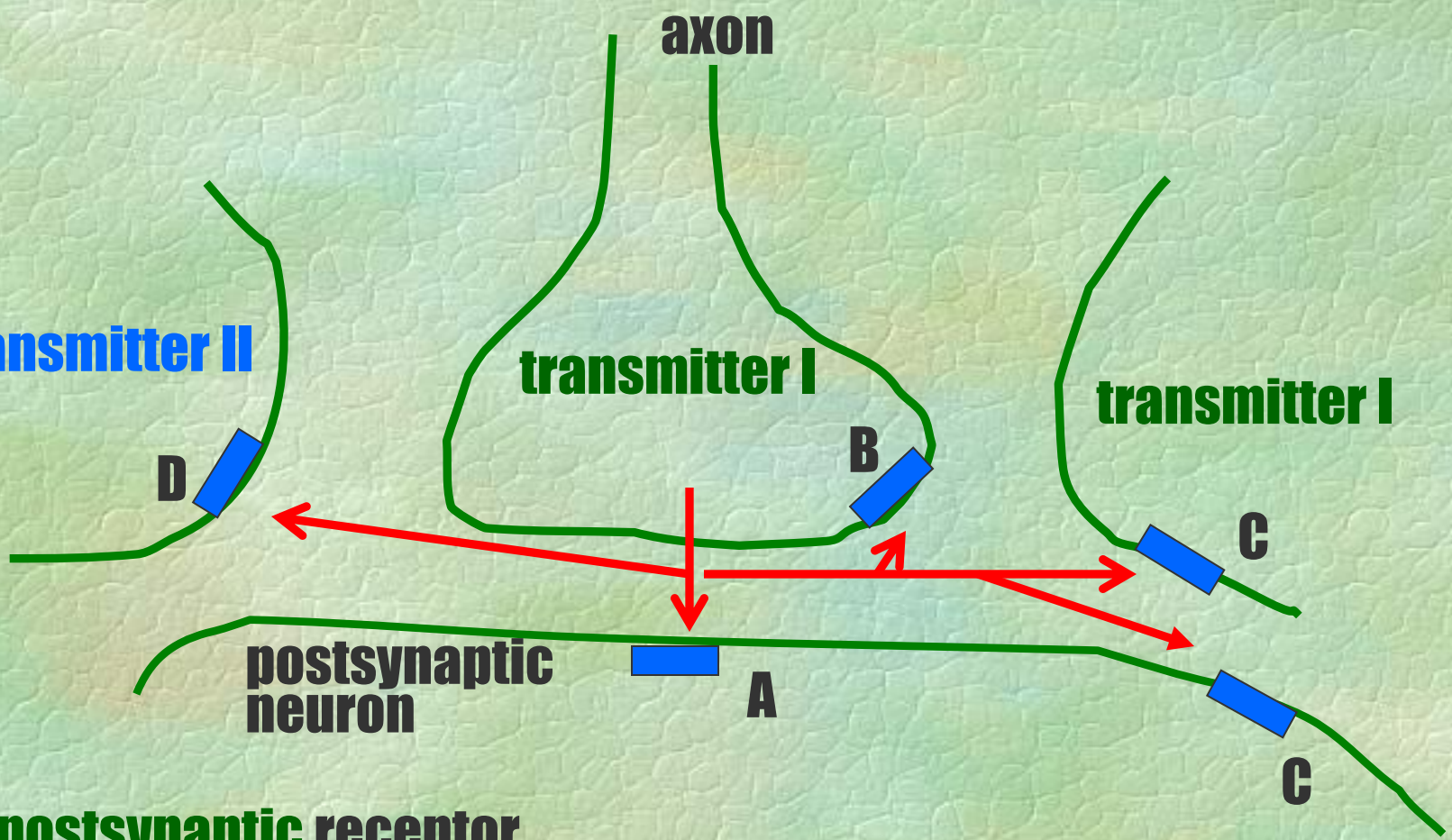
antagonist $5HT_{2C}$



glandula pienalis (melatonin - receptors: MT1, MT2, MT3)

melatonin

Guardiola-Lemaitre B at al. Br J Pharmacol. 2014; 171(15): 3604–3619



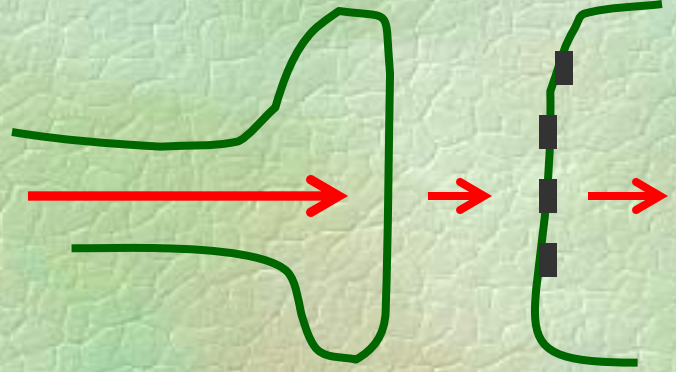
A - postsynaptic receptor

B - autoreceptor (presynaptic)

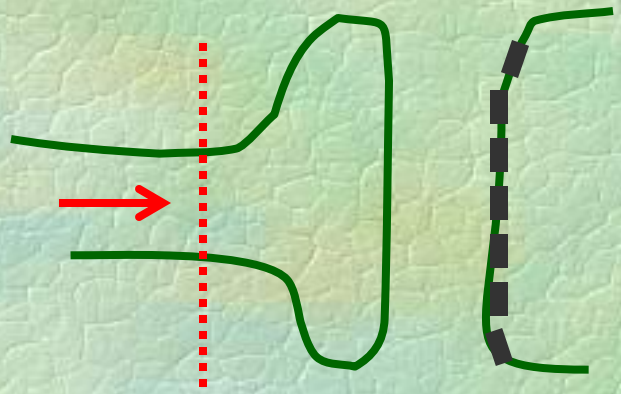
C - homoreceptor

D - heteroreceptor

Potential targets for transmitter release from nerve terminal

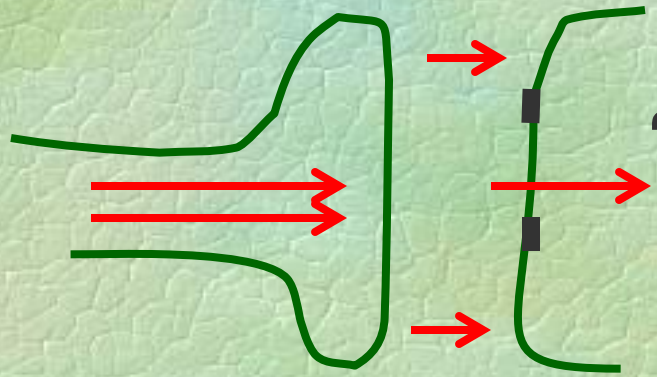


chronic effect of antagonists



“up-regulation” of receptors

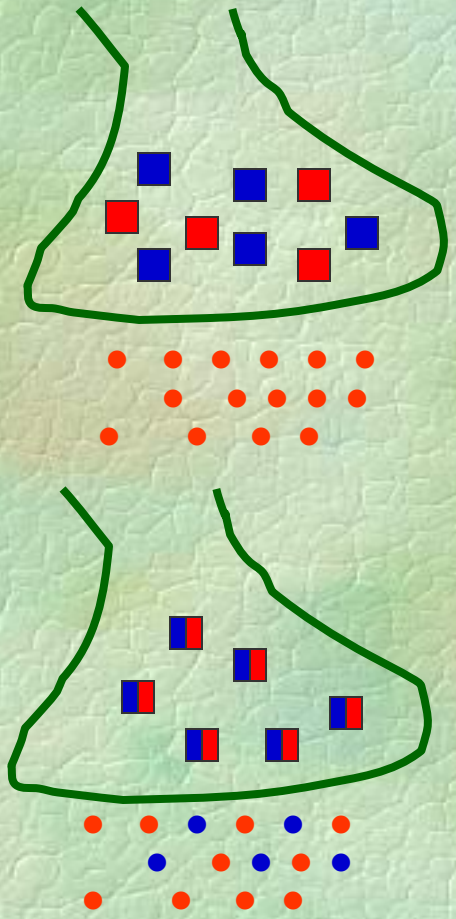
chronic effect of agonists

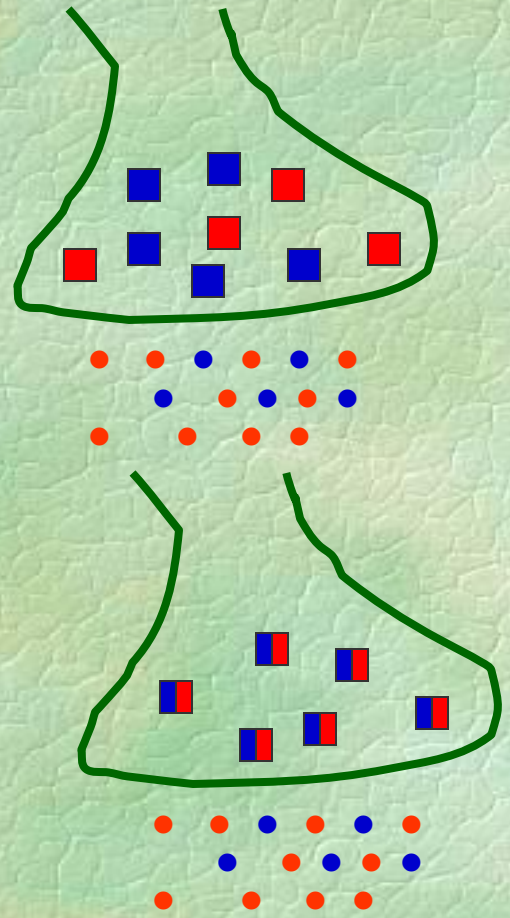


“down-regulaction” of receptors

CO-TRANSMISSION

stimulation frequency





Co-transmission

- co-transmitters stored in the same vesicles; convey different messages to different receptors at the same time
- co-transmitters stored in the differential vesicles; released preferentially in response to different frequency nerve impulses

Exogenic influences affecting just one transmitter cannot simulate the physiological synaptic effects

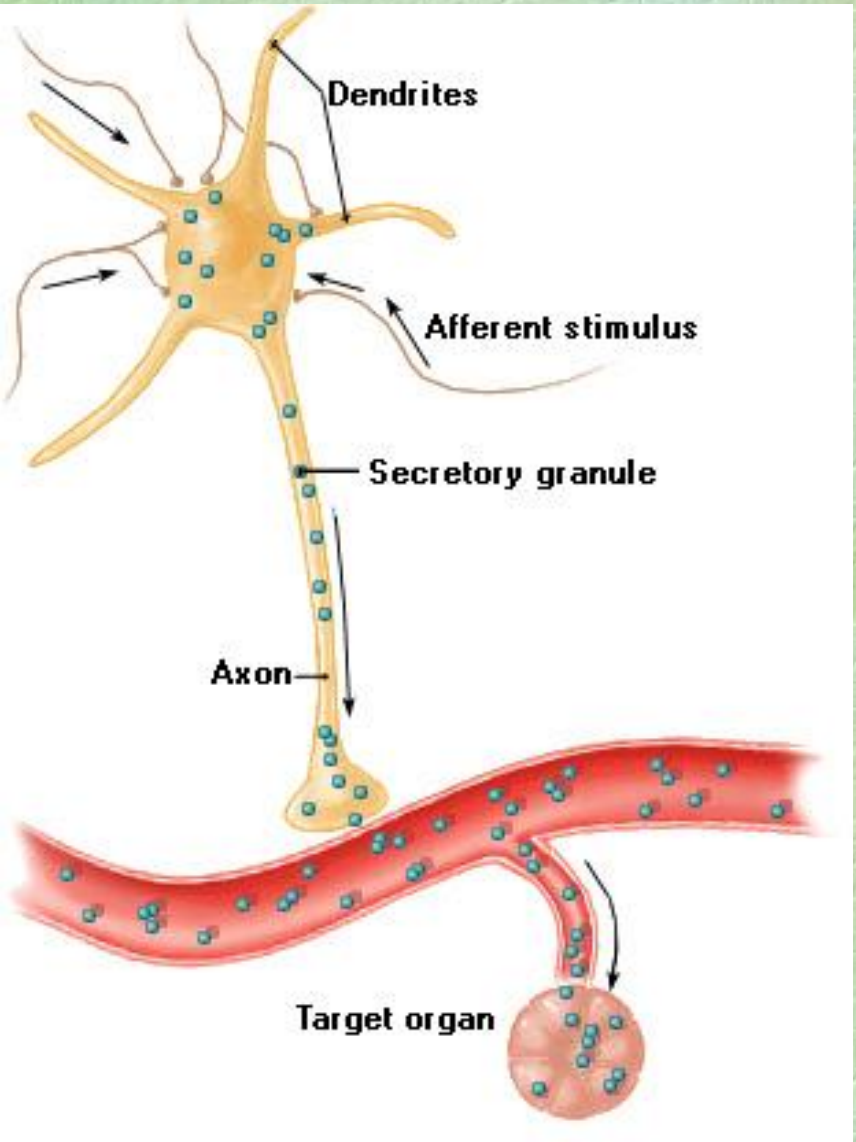
Other neurotransmitters, co-transmitters, neurohormones

endogenic opioids (enkefaline, endorphine, dynorphine) ↑ euforia
↓ anhedonia

cholecystokinine (CCK) ↑ satiety, panic disorder
↓ hunger

angiotensine
gastrine
neurokinines
neuropeptide Y
neurotensin
substance P
bradykinine
somatostatin
.....
.....

neurotransmitters released by nerve cells into blood circulation



NEUROHORMONES

e.g.:
oxytocine vasopressin,
gonadotropin, corticotropin . . .

NEUROMODULATORS (e.g. opioids, anandamide, NO ...)

biologically active in small amounts,

released on synapses, however, also by e.g. glial cells,

have impact on receptor activity either directly
or through interaction with neurotransmitter

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NEW NOMENCLATURE OF NEUROPSYCHOTROPICS

PROPOSED TEMPLATE FOR A MULTI-AXIAL PSYCHOPHARMACOLOGICAL NOMENCLATURE

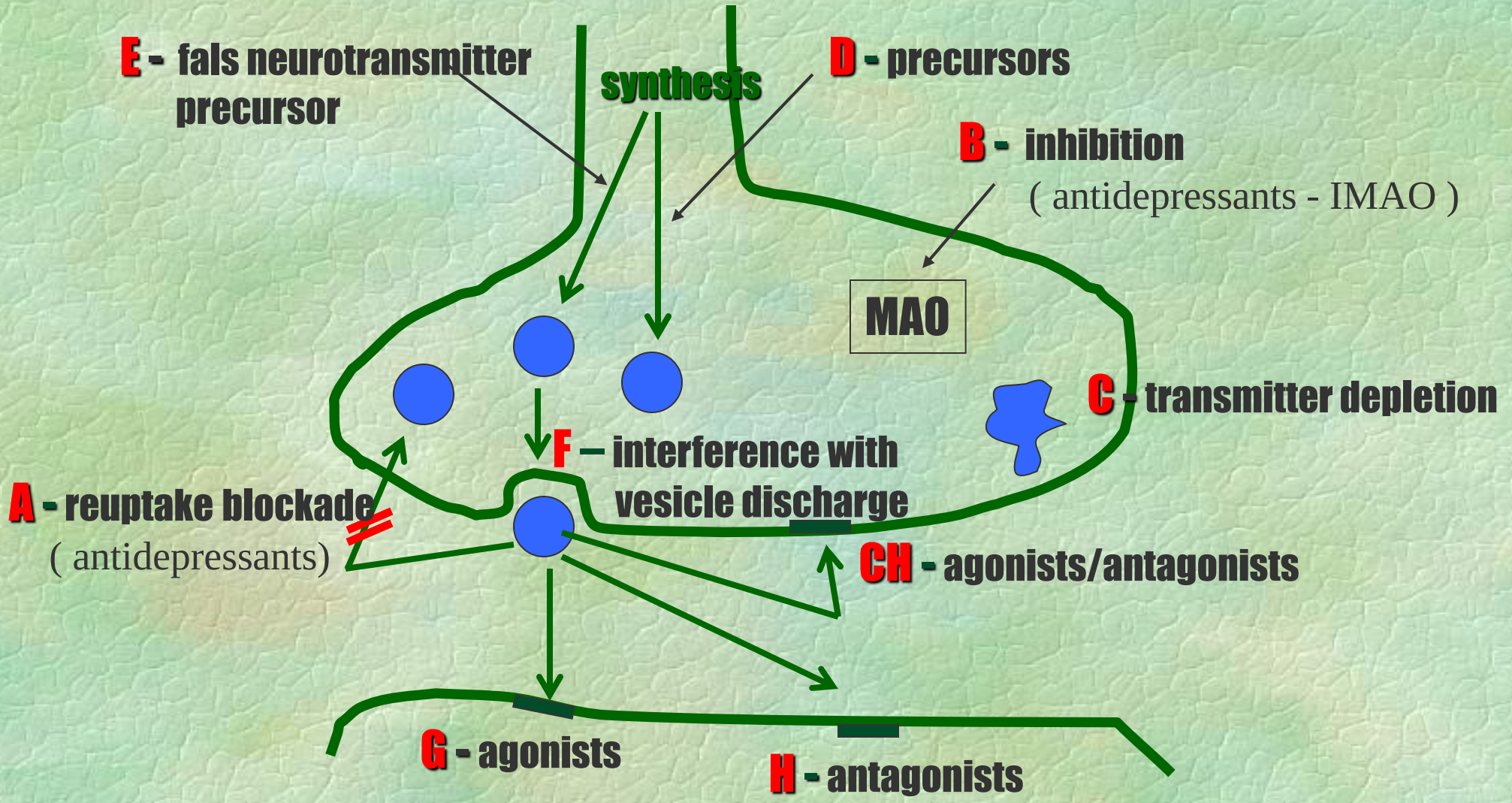
Axis 1 . . .

Axis 2 Family (primary neurotransmitter(s) and relevant mechanism)

Axis 3 . . .

Axis 4 . . .

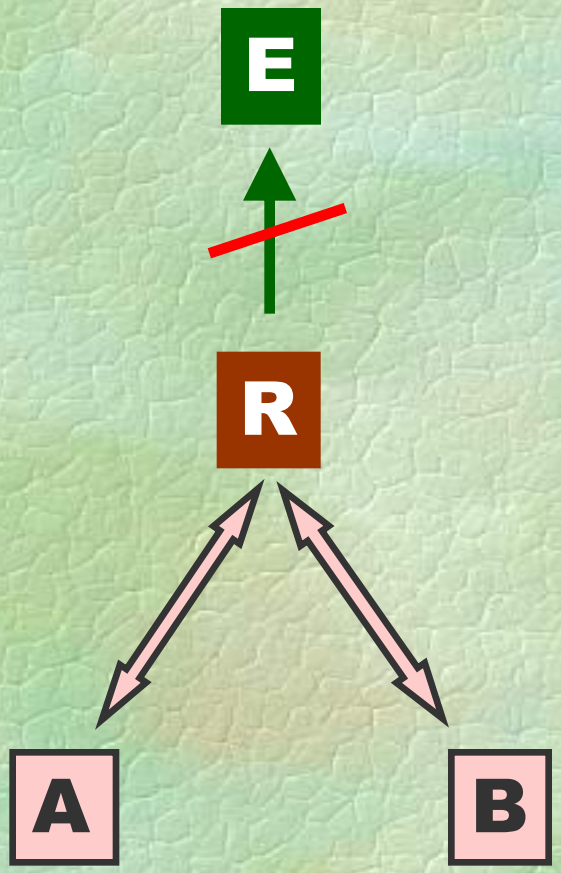
Axis 5 . . .



Sites of drug action at the synapse

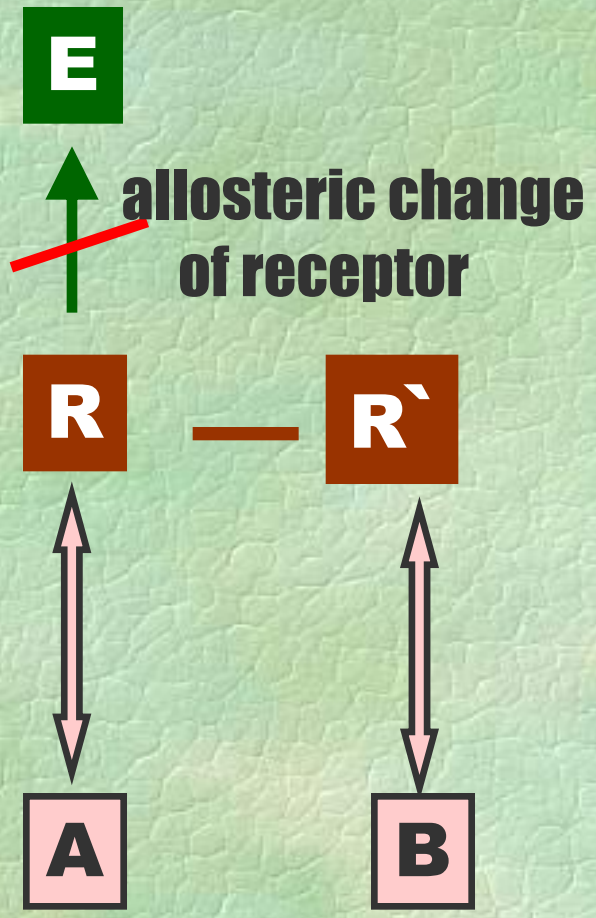
→ DIRECT - G, H, CH

↘ INDIRECT - A, B, C, D, E, F



A = agonist

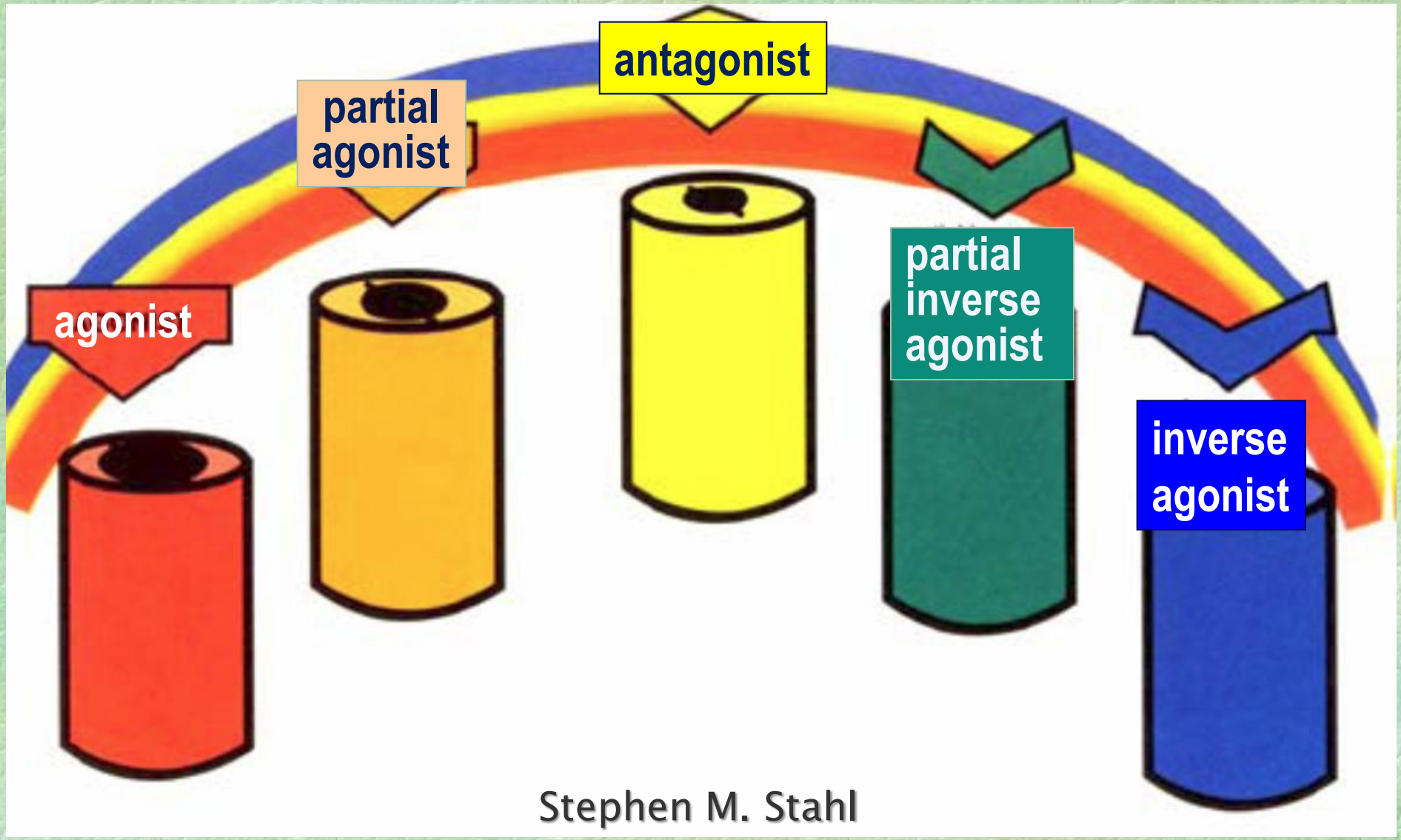
B = antagonist



ANTAGONISMUS
competitive
and
specific noncompetitive

ANTAGONISM
noncompetitive
nonspecific

LIGANDS of RECEPTORS



TYPES of RECEPTOR LIGANDS

agonist

partial agonists (competitive dualist)

antagonist — competitive

— noncompetitive

- specific
- nonspecific

inverse agonist

partial inverse agonist

AGONISTIC LIGANDS	EFFECTS
agonist	maximal receptor activation
partial agonist	none full activation
inverse agonist	inactivation of receptors constitutively active

ANTAGONISTS	EFFECTS
competitive	reversibile receptor blockade
noncompetitive (specific)	irreversibile receptor blockade
noncompetitive (nonspecific, allosteric)	reversibile or irreversibile binding to different binding site closely to receptor active site

Psychotropics
with inverse agonistic receptor mechanism of action, e.g.:

CB1 cannabinoid receptors …. rimonabant

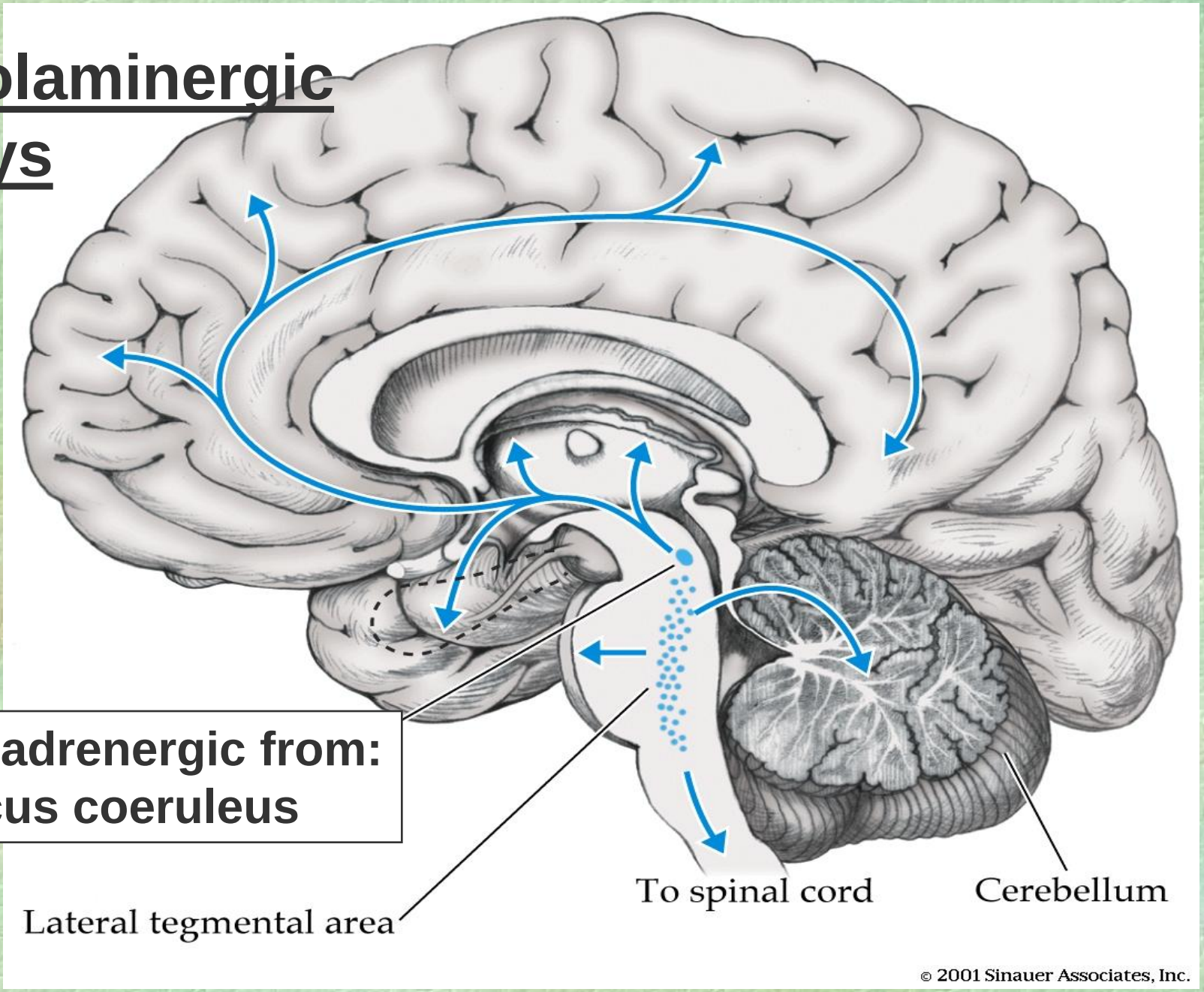
μ opioid receptors …. naloxon

5HT receptors …chlorpromazine, risperidone, mirtazapine

Effects of benzodiazepine receptor ligands

agonist	partial agonist	antagonist	partial inverse agonist	inverse agonist
anxiolytic	anxiolytic	žádný klinický	promnestický	promnest
sedative/ hypnotic			anxiogenní	anxio
myorelaxant			prokonvulsivní	
antikonvulsive				
amnestic				
dependence				

Catecholaminergic pathways



Catecholamines

dopamine (basal ganglia, limbic system . . .)
noradrenaline (hypothalamus, cortex, cerebellum)
adrenaline

synthesis tyrosine → tyrosine hydroxylase ⇒ DOPA → decarboxylase ⇒ dopamine → hydroxylasea ⇒ noradrenaline → N-methyltransferase ⇒ adrenaline

storage - in vesicles (with ATP - 4 : 1)
- free in cytoplasmic fluid

breakdowb - re-uptake !!
- diffusion
- intracellularly - MAO_A (A a Na) + MAO_B (DA)
  extracellularly - MAO_B + COMT

Catecholamines

continuation

receptors

DA r. - partly sensitive to A a Na, too

$D_{1, 5}$ - coupled to adenylylcyclase → ↑ cAMP – excitation

$D_{2, 3, 4}$ - coupled to phosphodiesterase (cAMP degradation) - ↓cAMP - inhibition

adrenergic r. (in the CNS in neurons; on vessels)

- α

  α_1 - stimulation of phosphatidylinositol metabolism

  α_2 - ↓ cAMP
  ↑ K^+ channel
  ↓ Ca^{2+} channel
  } regulated by G-protein

- $\beta_{1, 2, 3}$ - ↑ cAMP

Known co-transmissions with DOPAMINE

- DA + cholecystokinin (CCK)
- DA + neurotensin
- DA + galanin
- DA + dynorphin
- DA + Met-enkephalin
- DA + Leu-enkephalin
- DA + GH-RH (hormon uvolňující růstový hormon)

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NOVÁ NOMENKLATURA NEUROPSYCHOTROPIK

PROPOSED TEMPLATE FOR A MULTI-AXIAL PSYCHOPHARMACOLOGICAL NOMENCLATURE

Axis 1 . . .

Axis 2 . . .

Axis 3 . . .

Axis 4 . . .

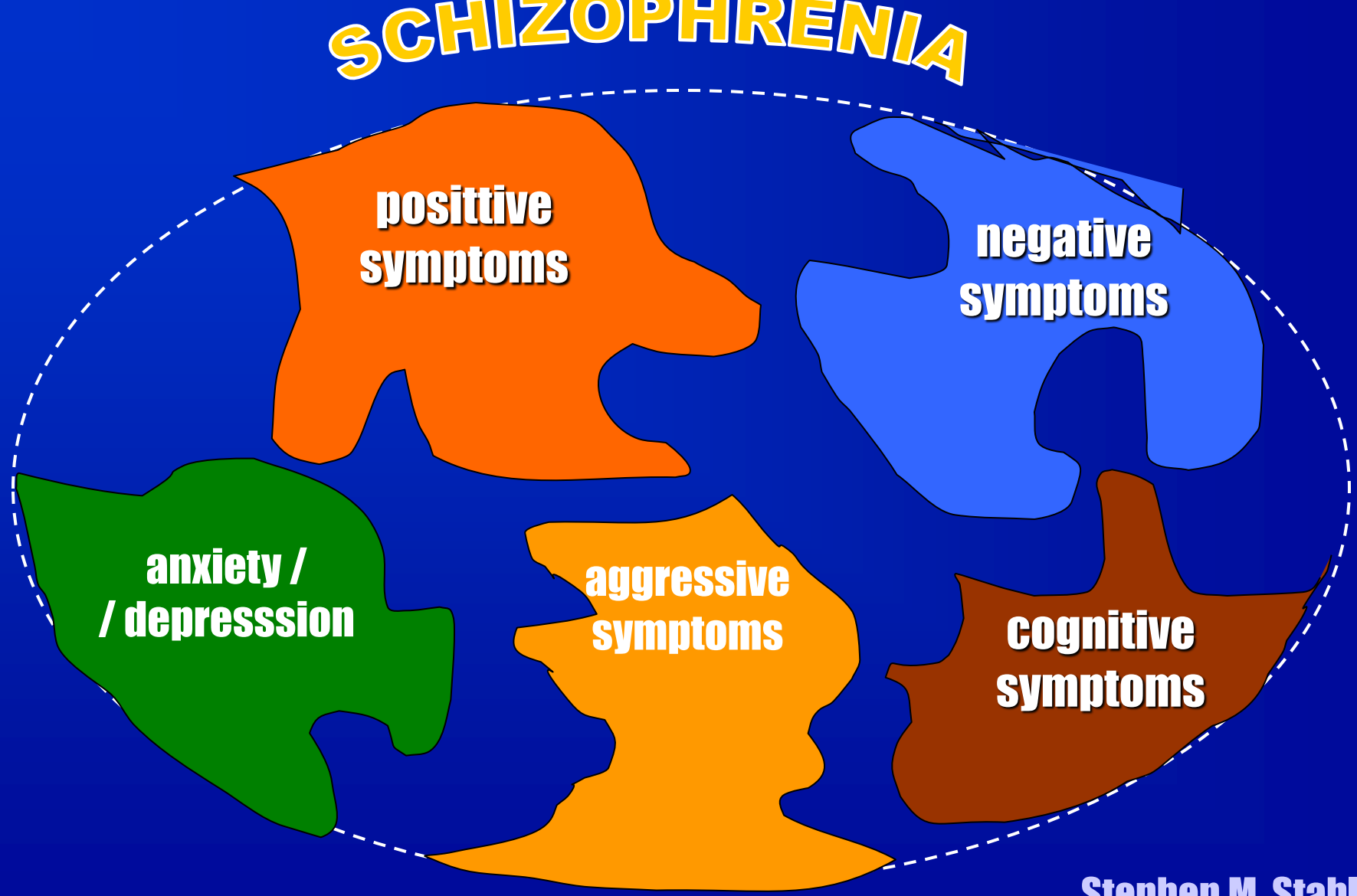
Axis 5 Indication

PSYCHOSIS

- **a person's capacity, affective response to recognize reality, communicate, and relate to others is impaired**

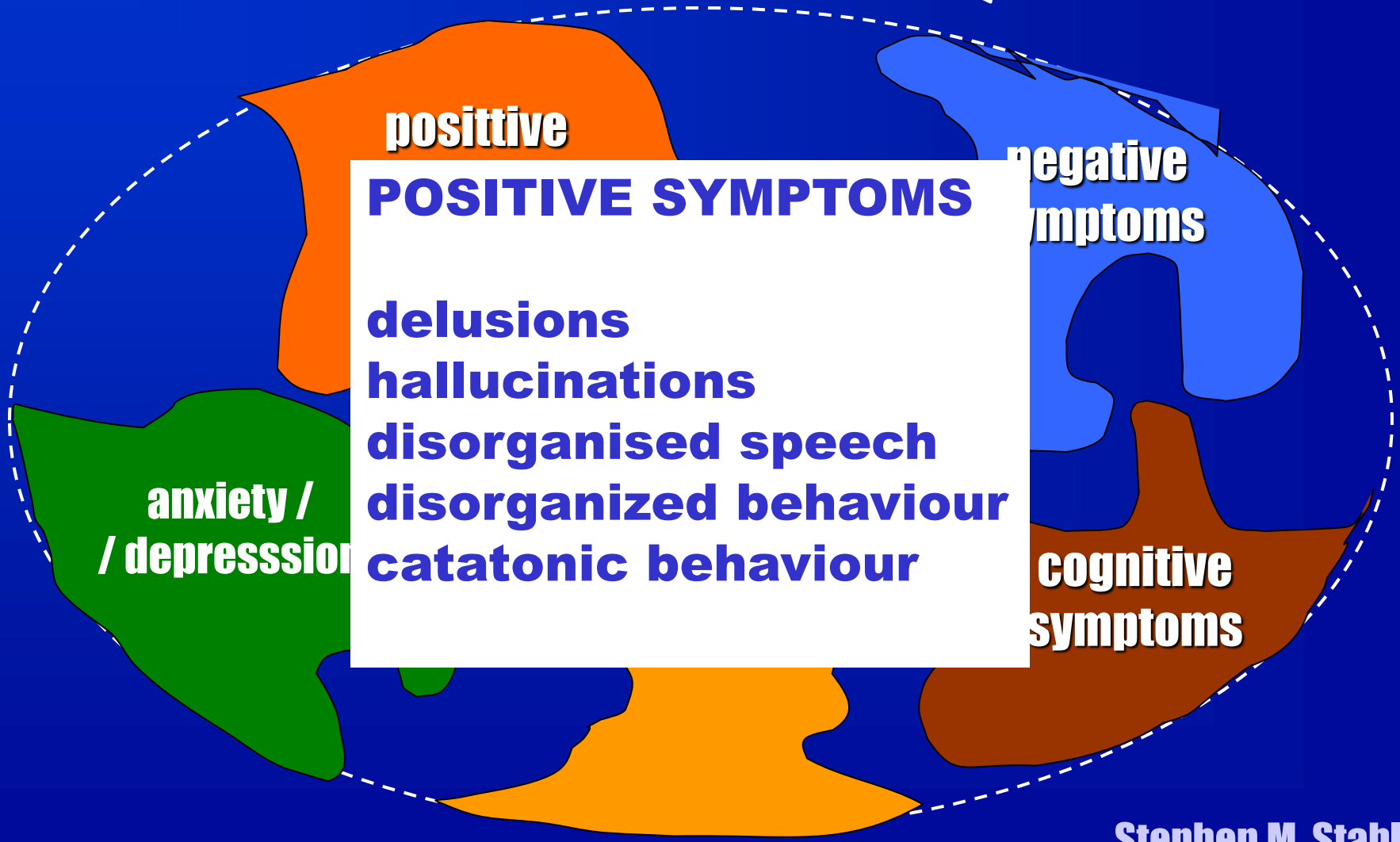
- **schizophrenia,**
- **mania,**
- **depression,**
- **Alzheimer's dementia**
- **cognitive disorders**

hallucinations (auditory, visual, olfactory, gustatory, tactile**)**
delusions (misinterpretations of perceptions or experiences**)**



Stephen M. Stahl, 2000

SCHIZOPHRENIA

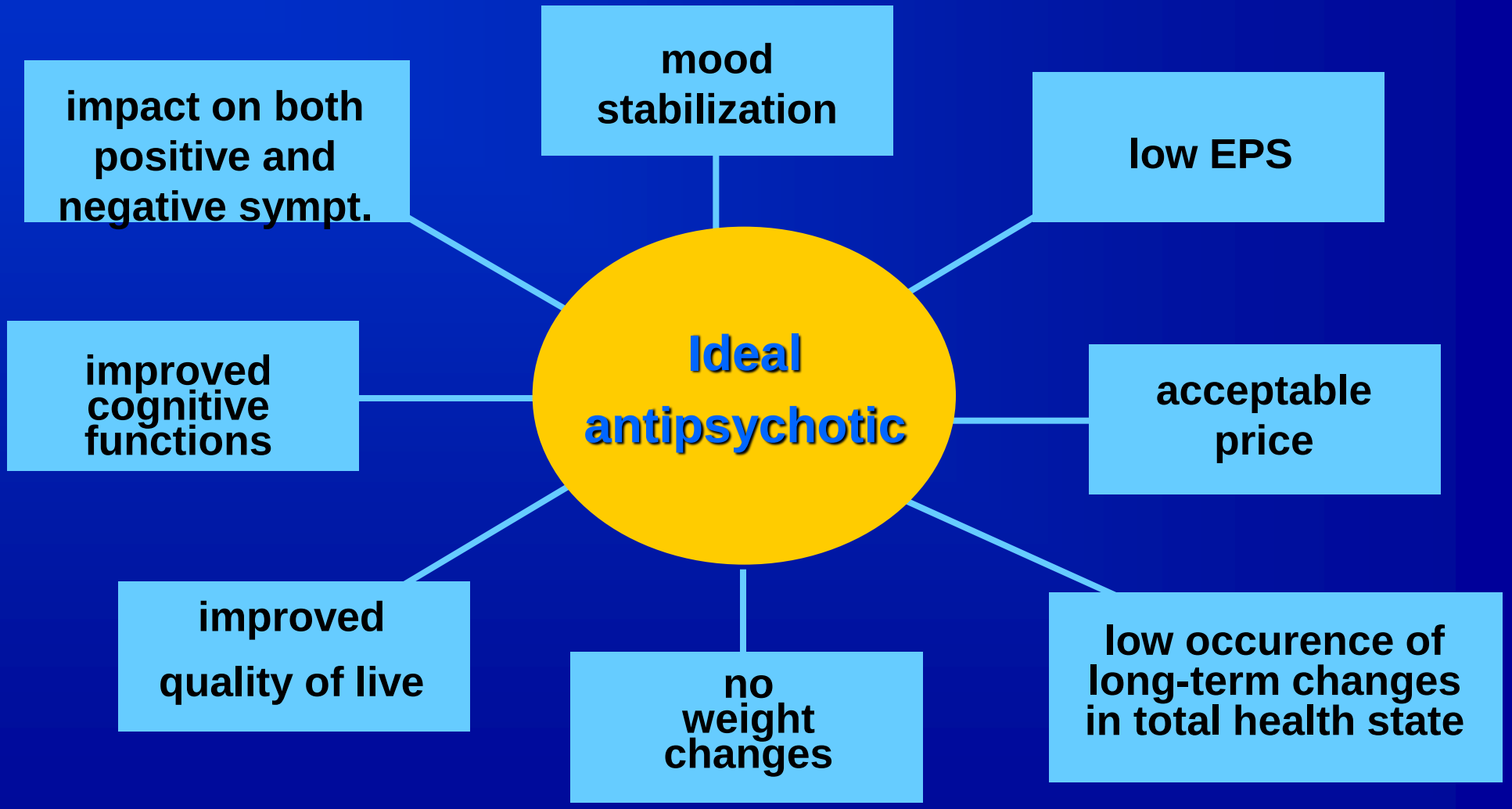


POSITIVE SYMPTOMS

delusions
hallucinations
disorganised speech
disorganized behaviour
catatonic behaviour

Stephen M. Stahl, 2000

Ideal antipsychotic drug effects



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NOVÁ NOMENKLATURA NEUROPSYCHOTROPIK

PROPOSED TEMPLATE FOR A MULTI-AXIAL PSYCHOPHARMACOLOGICAL NOMENCLATURE

Axis 1 . . .

Axis 2 . . .

Axis 3 Neurobiological activities

Animal Human Neurotransmitter effects

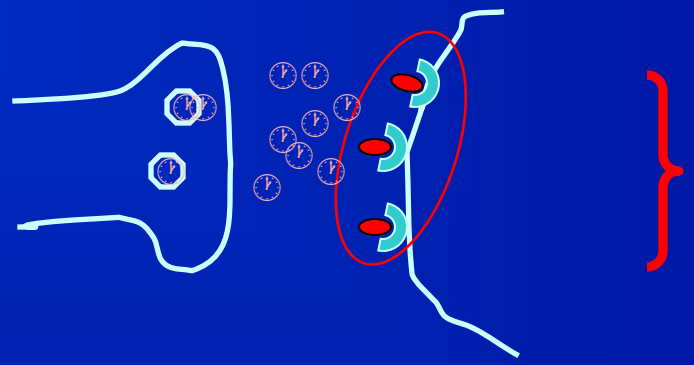
Brain circuits Physiological

Axis 4 . . .

Axis 5 . . .

Blocking of postsynaptic dopamine receptors D_2

in psychosis



- D_2 antagonist

SUPPRESSION OF POSITIVE SYMPTOMS

"Dopaminergic hypothesis of schizophrenia"

Dopamine receptor subtypes

DA r. – partly sensitive to Adrenaline and Noradrenaline, too

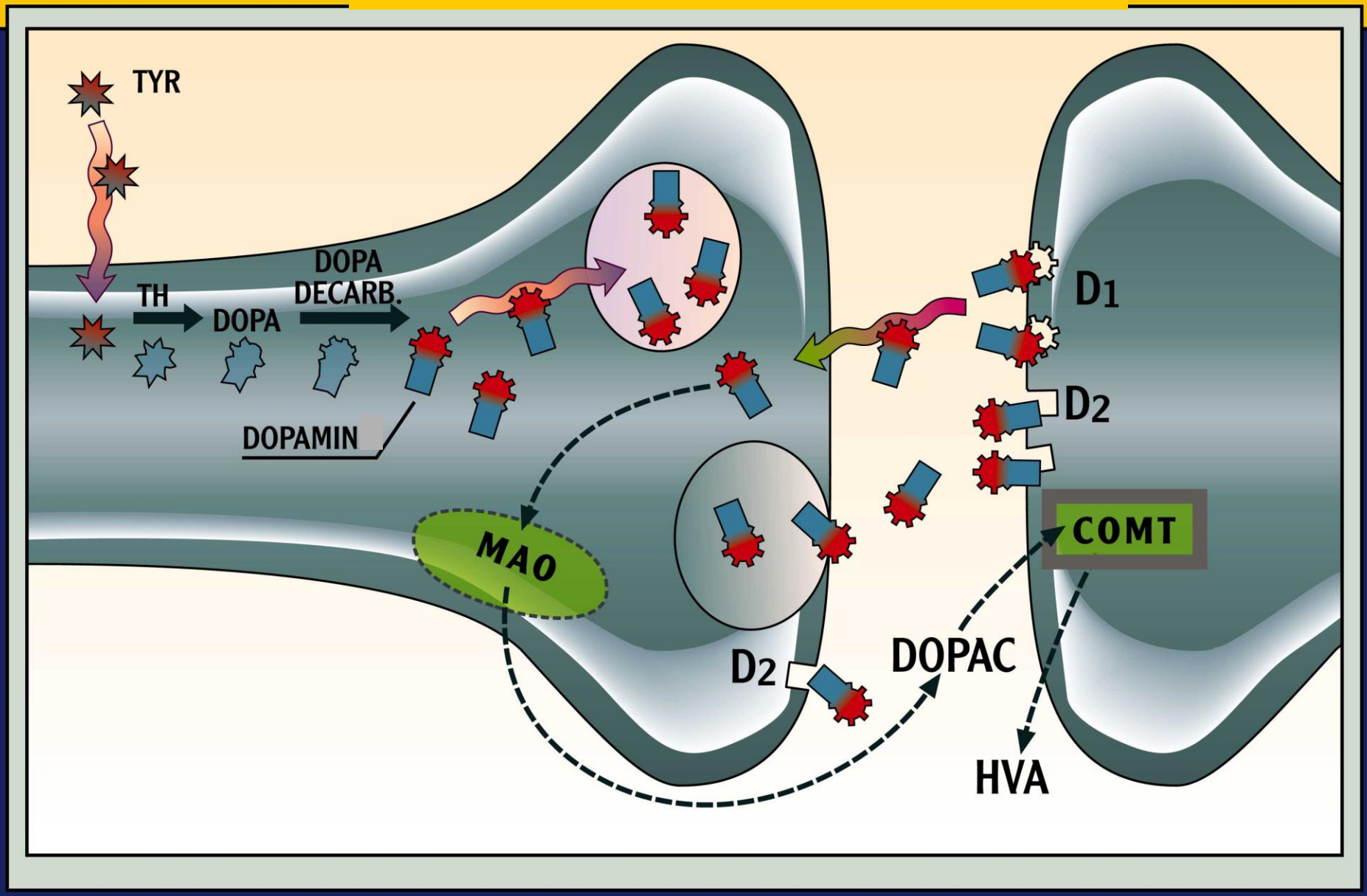
Family D1:

$D_{1, 5}$ - coupled to adenylylcyclase → ↑ cAMP – excitatory influence

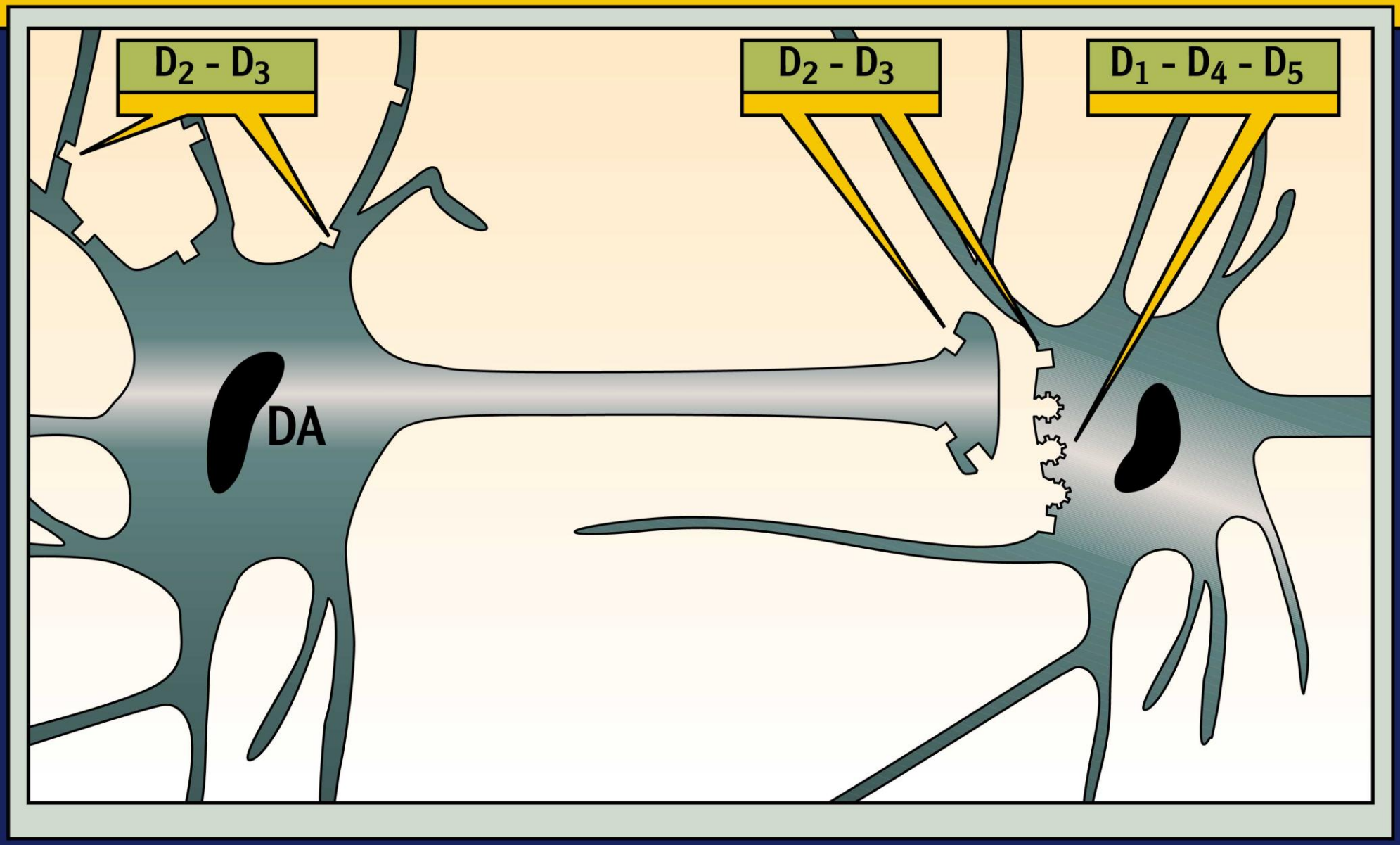
Family D2:

$D_{2, 3, 4}$ - coupled to phosphodiesterase (cAMP degradation) → ↓ cAMP - inhibitory influence

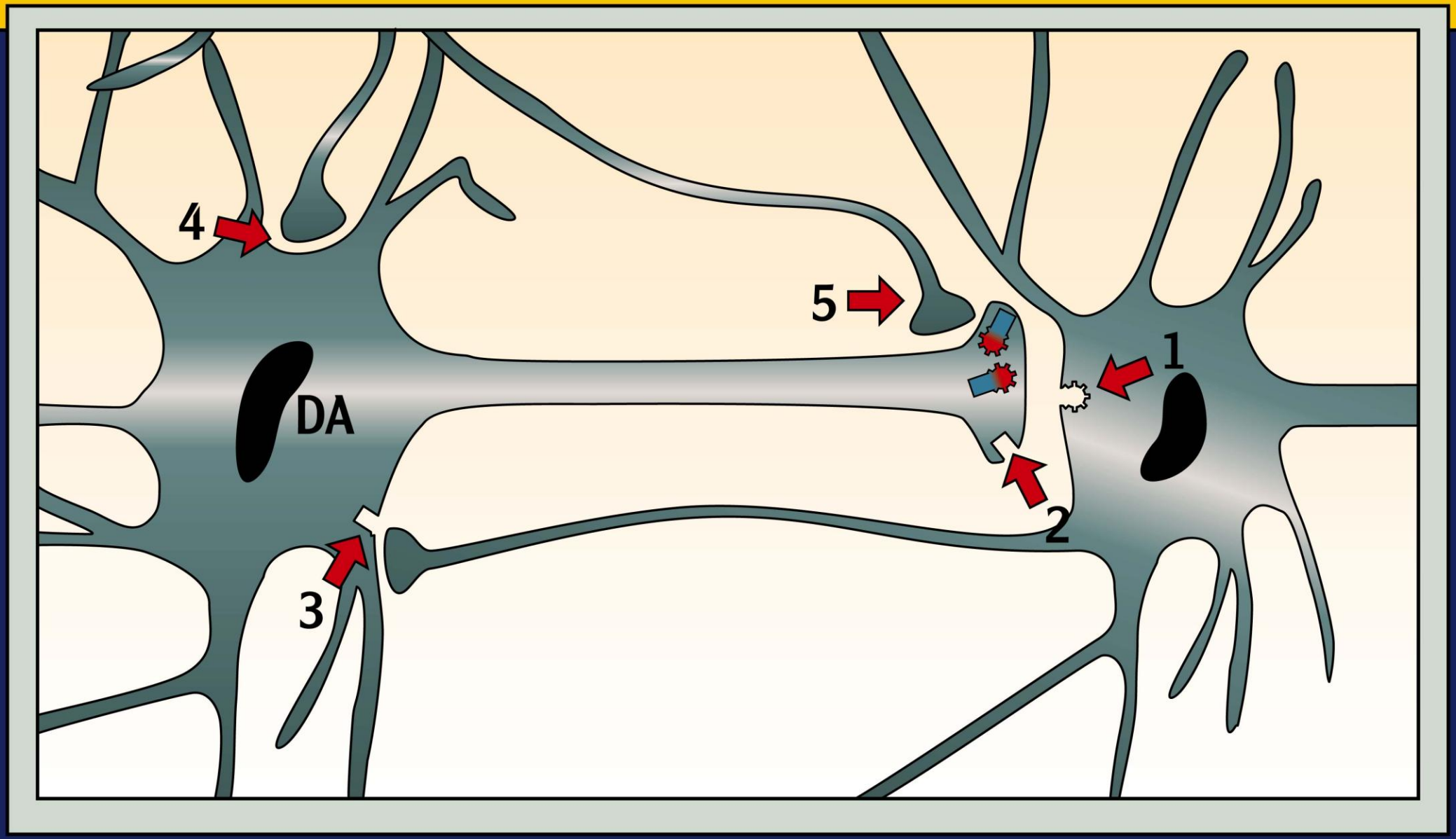
Dopaminergic neurotransmision



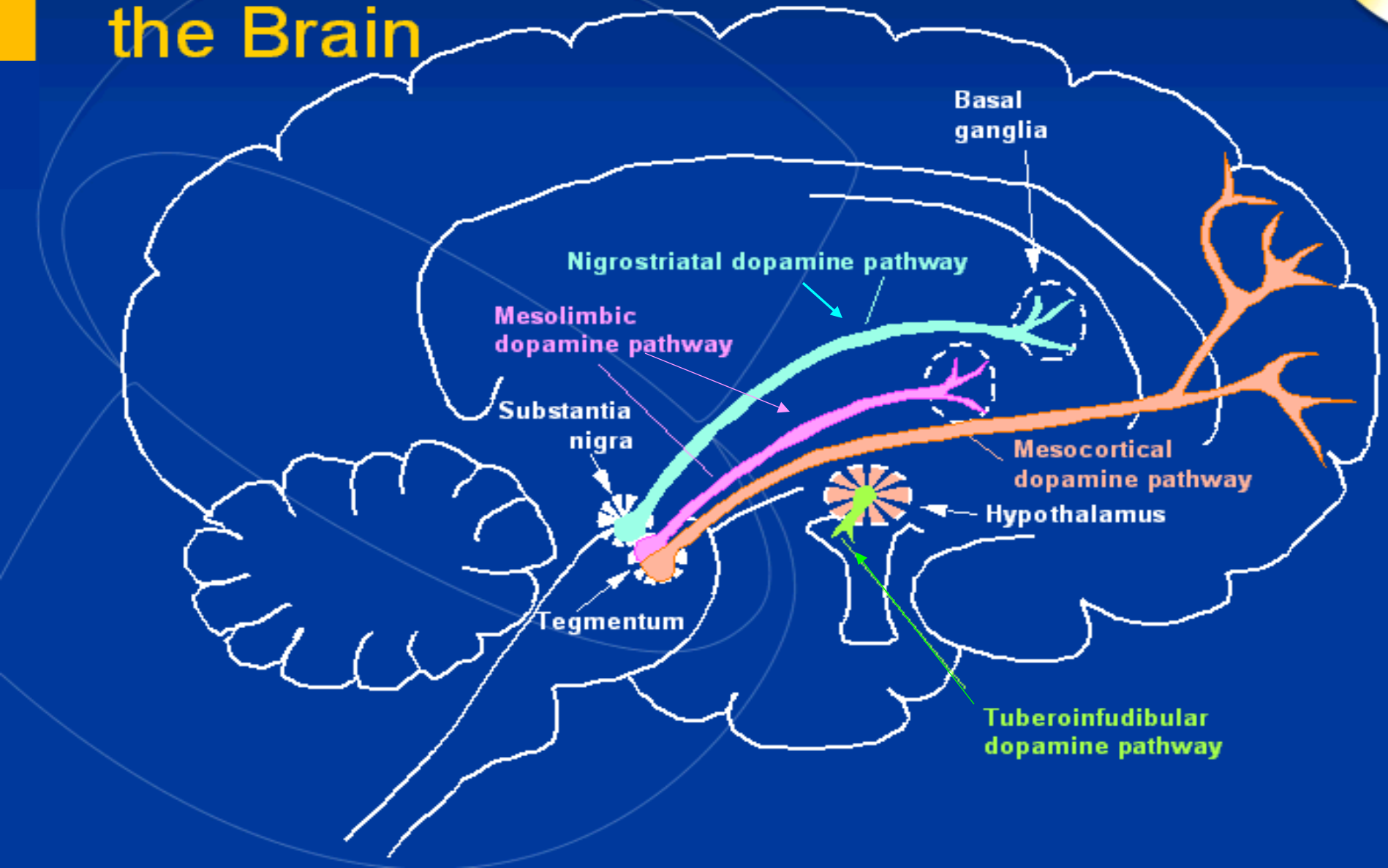
Dopamine receptors



Possible modulation of dopaminergic transmistter functions



The 4 Dopaminergic Pathways of the Brain



4 DAergic brain pathways

NIGROSTRIATAL (subt. nigra – basal ganglia)
control of movements

MESOLIMBIC (midbrain VTA – ncl. accumbens)
positive symptoms, euphoria

MESOCORTICAL (midbrain – limbic cortex)
negative symptoms,
cognitive side effects

TUBEROINFUNDIBULAR
(hypothalamus – anterior pituitary gland)
control of prolactine secretion

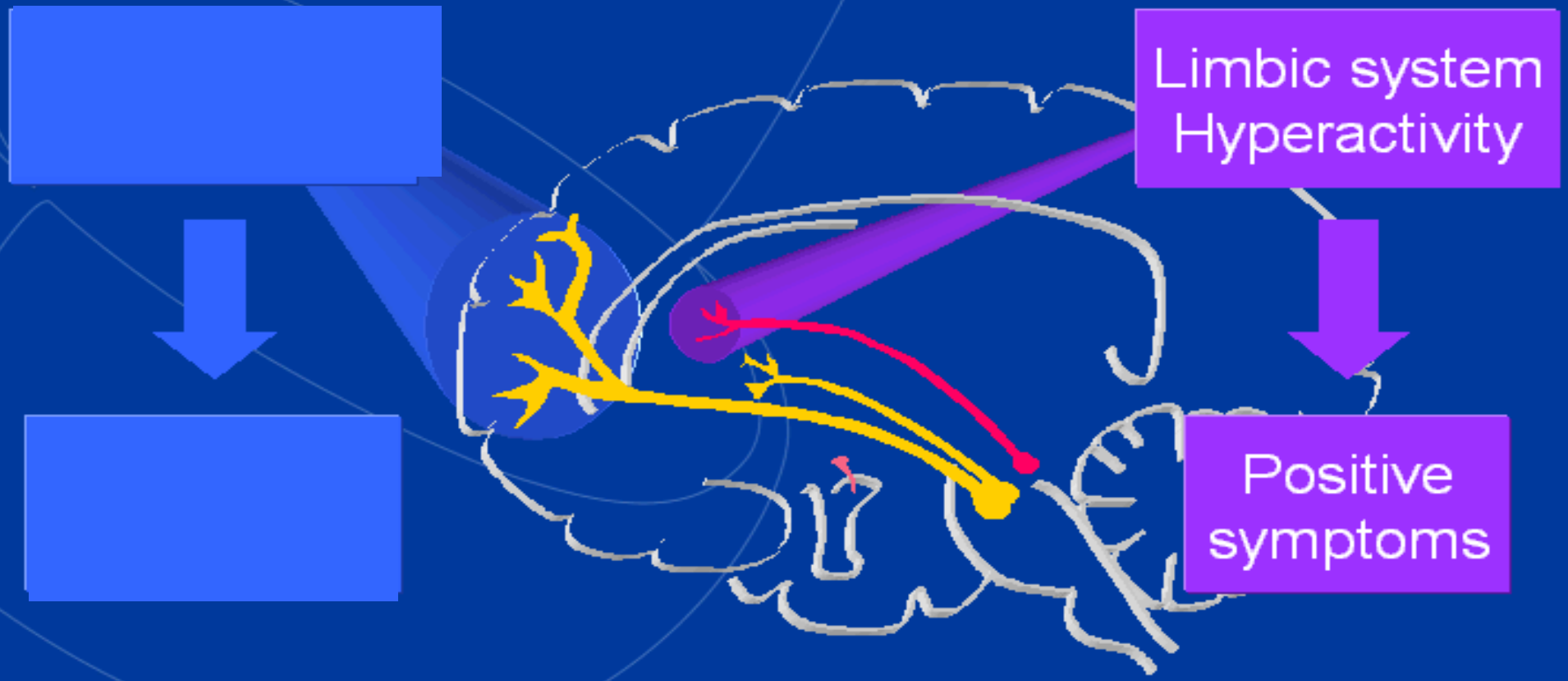
MAIN SYMPTOMS OF SCHIZOPHRENIA

POSITIVE SYMPTOMS

delusions
hallucinations
disorganised speech
disorganized behaviour
catatonic behaviour

The Dopamine Hypothesis of Schizophrenia

Mesofrontal and Mesolimbic Dopamine Pathways



MAIN SYMPTOMS OF SCHIZOPHRENIA

POSITIVE SYMPTOMS

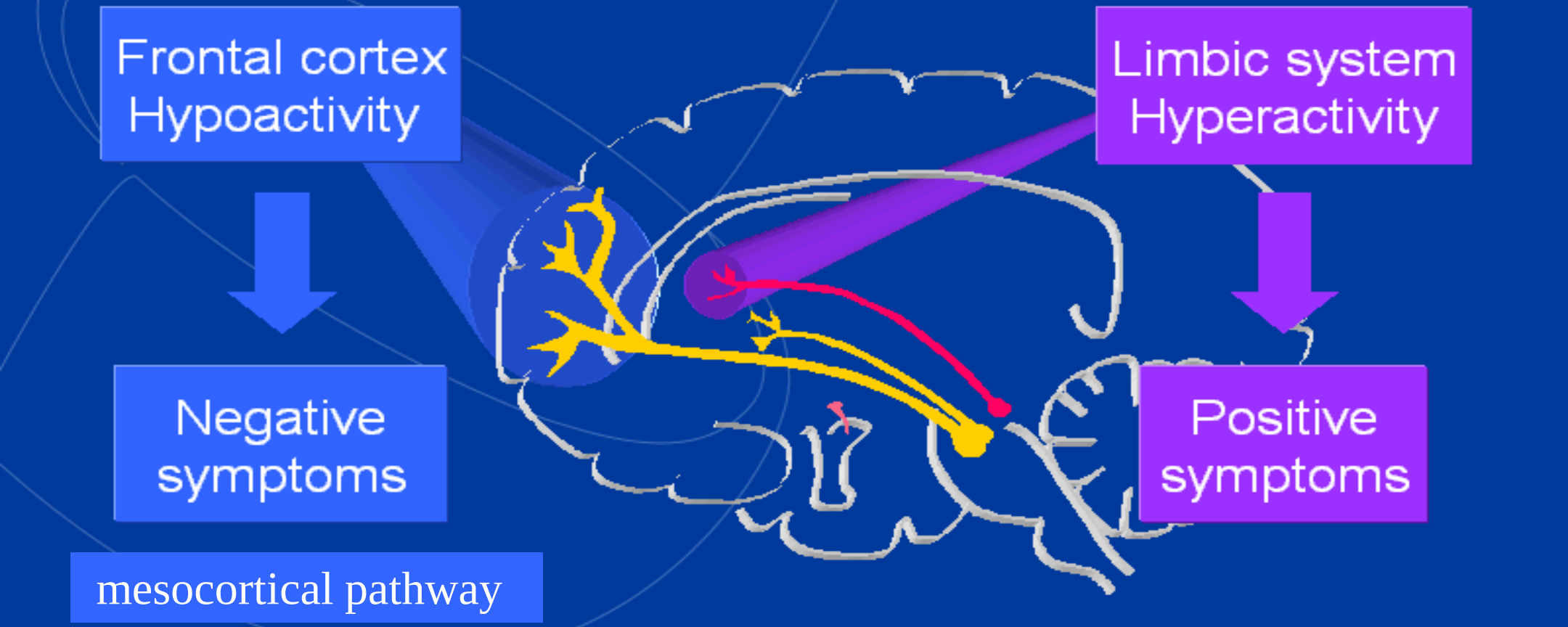
delusions
hallucinations
disorganised speech
disorganized behaviour
catatonic behaviour

NEGATIVE SYMPTOMS

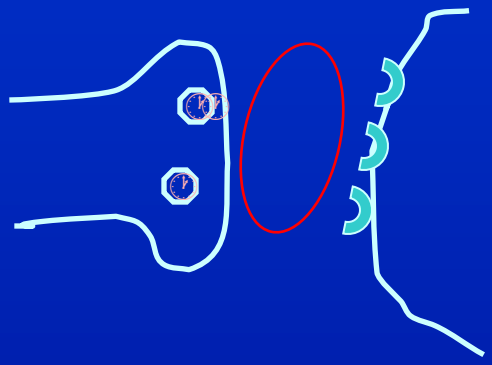
affective flattening (restriction of emotional expression)
alogia
avolition (general lack of desire, motivation, difficulty, or inability to initiate and persist in goal-directed behaviour)
anhedonia (lack of pleasure)
attention impairment

The Dopamine Hypothesis of Schizophrenia

Mesofrontal and Mesolimbic Dopamine Pathways

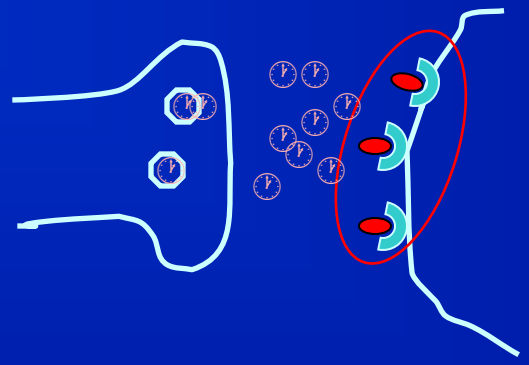


? ? Couses of hypoactivity of mesocortical DAergic pathway ??



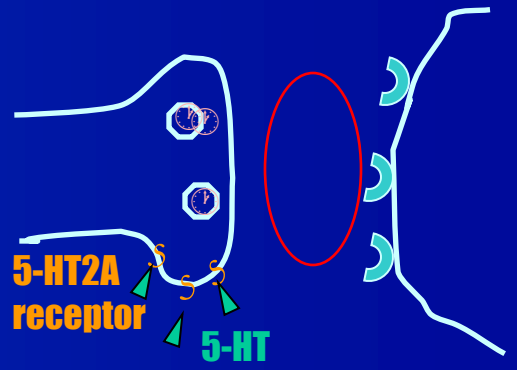
dopamine

Primary defficit
of dopamine



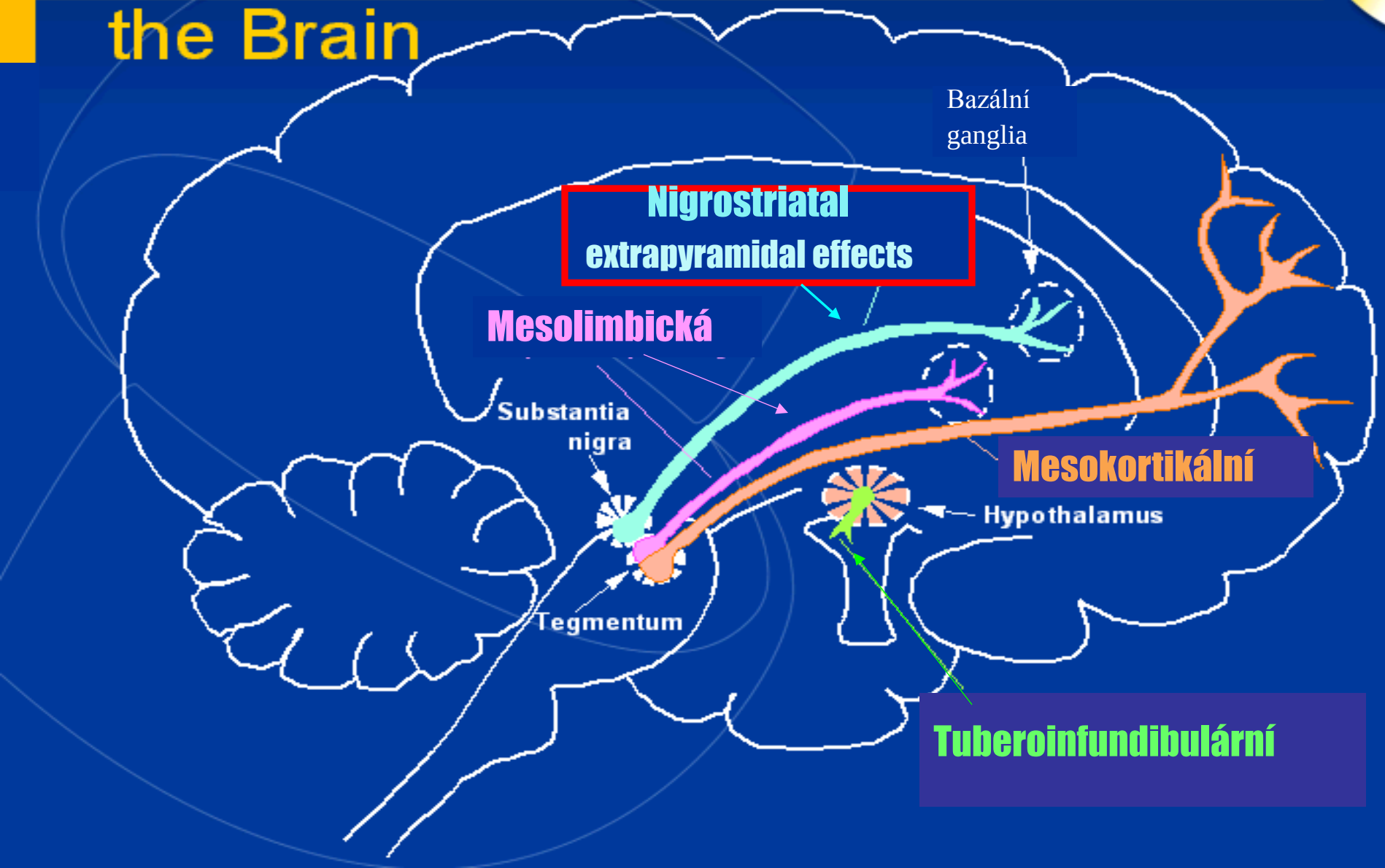
D2 antagonist

Blockade
of D2 receptors

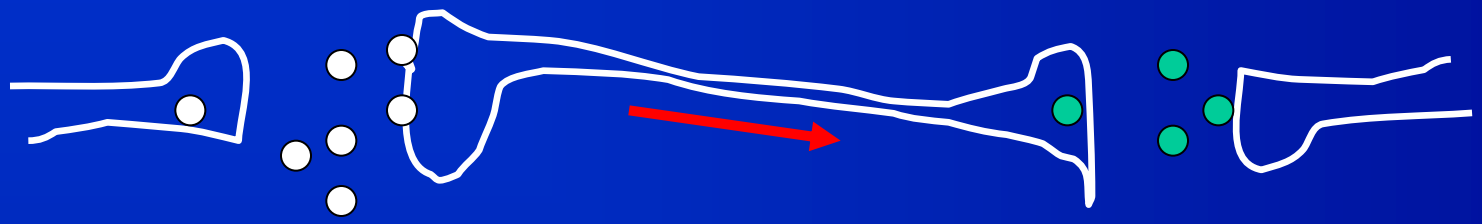


Secondary deficit
of dopamine

The 4 Dopaminergic Pathways of the Brain



nigrostriatal pathway → DA inhibits Ach activity



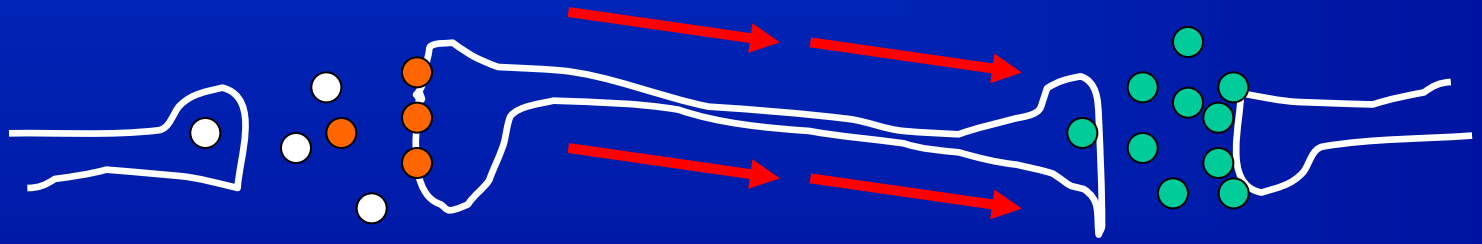
DA

Ach

antipsych.

anti-Ach

blockade of DA function → Ach hyperactive

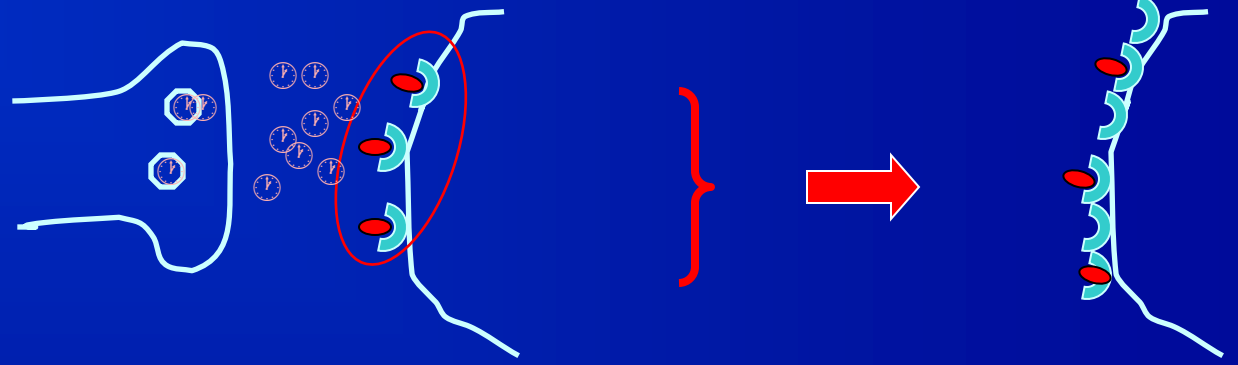


consolidation of Ach hyperactivity

Nigrostriatal dopaminergic pathway

EPS

Tardive dyskinesia



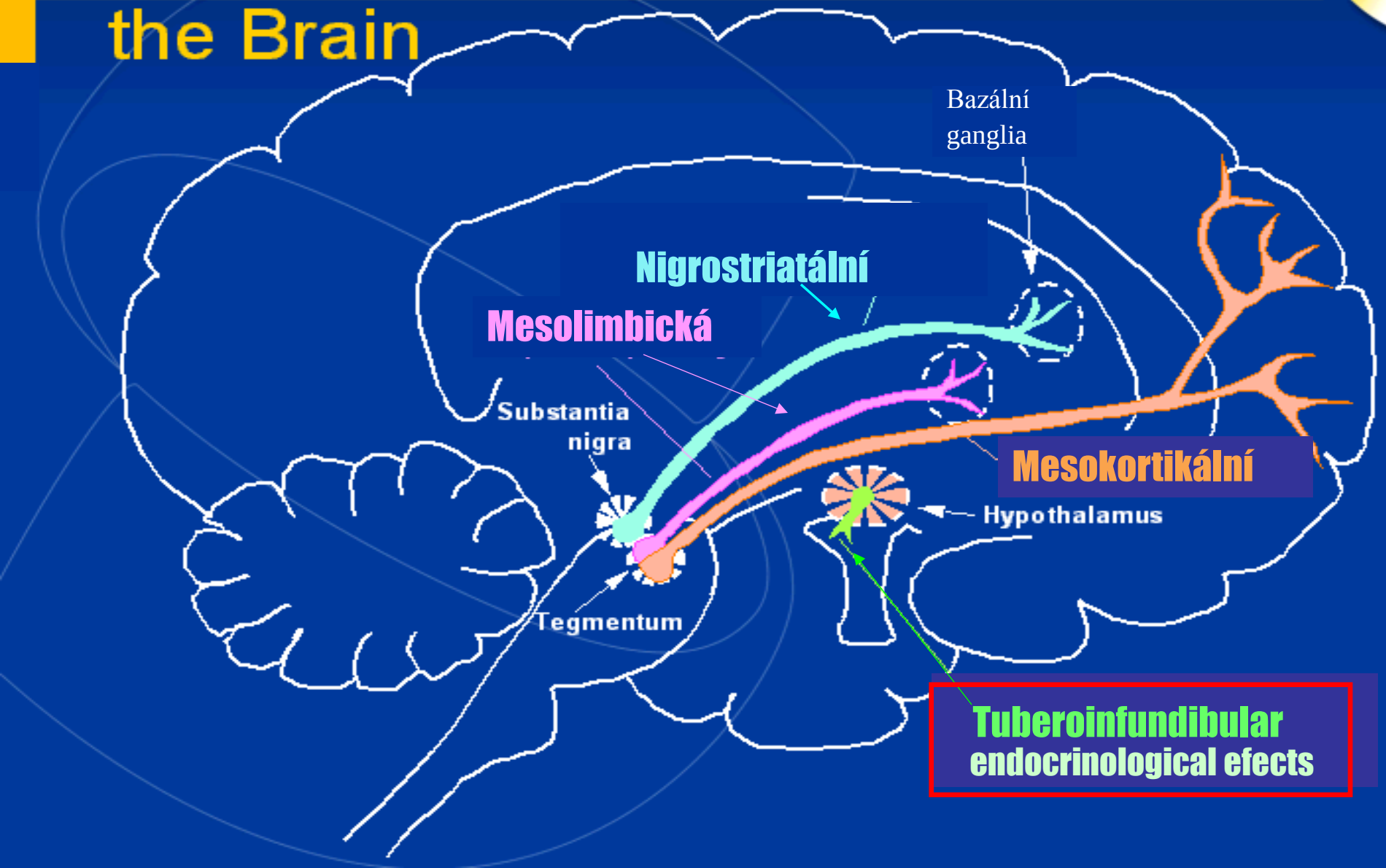
D2 antagonist

Blockade of D2 recept. in nigrostriatal pathway

D2 receptor up-regulation

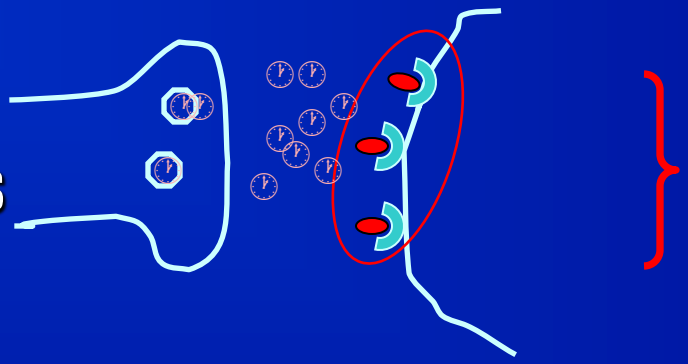
Stephen M. Stahl, 2000

The 4 Dopaminergic Pathways of the Brain



Tuberoinfundibular dopaminergic pathway

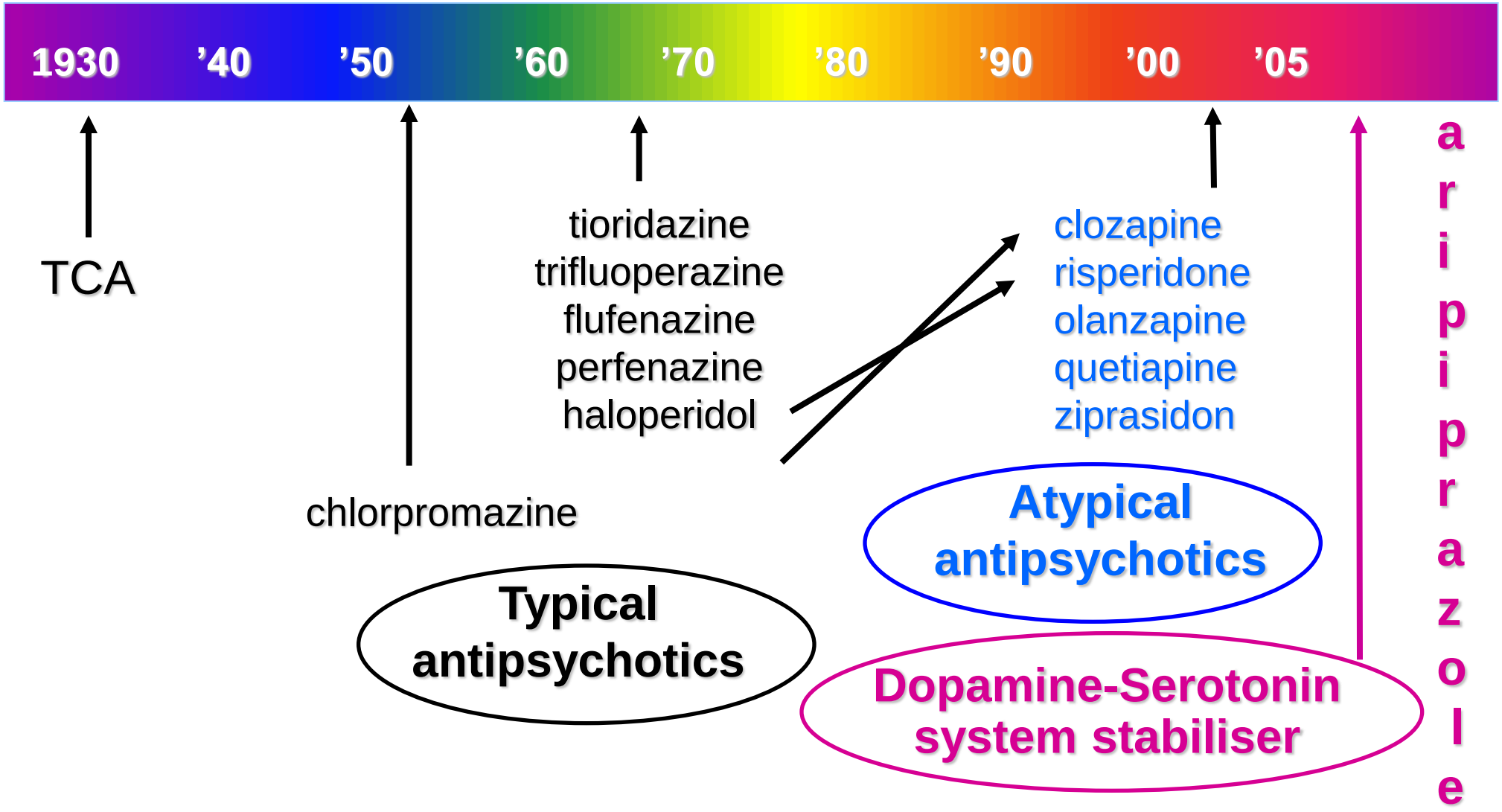
Blockade of D2 receptors



D2 antagonist

Hyperprolactinemia

Development of antipsychotics



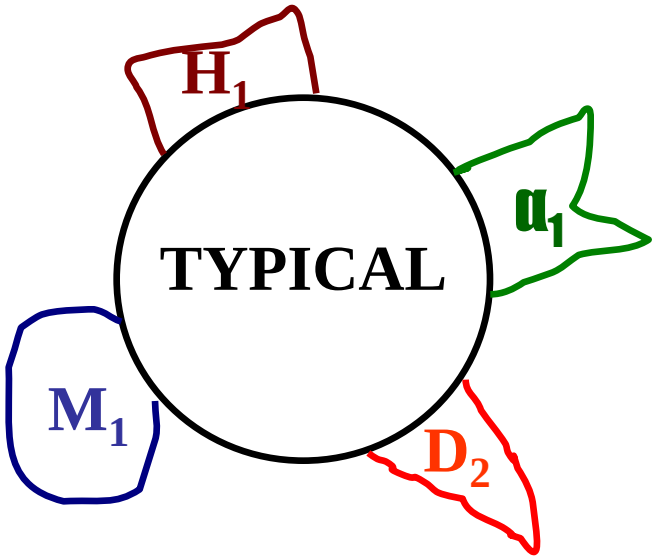
ANTIPSYCHOTICS (neuroleptics)

Typical (I. generation)

Basic (sedative): (***lower efficacy - doses in hundreds of mg***)
chlorpromazine, levomepromazine, chlorprothixen, thioridazine, clopenthixol

Incisive: (***higher efficacy - doses in mg or tens of mg***)
prochloperazine, phluphenazine, perphenazine, pimozide, haloperidol, flupenthixole
DEPOT (1x /1 – 3 weeks) – penfluridole, fluphenazine

ANTIPSYCHOTICS



D_2 blockade = antipsychotic effects
M_1 blockade = dry mouth, diplopia, constipation
α_1 blockade = ↓ BP, dizziness
H_1 blockade = drowsiness, weight gain

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Adverse effects: *EPS, tardive dyskinesia, prolactinemia, malignant neuroleptic syndrom*

Neuroleptic Malignant Syndrom

idiosyncratic response (20-30% mortality; in 1-2% treated patients)
5-10 day persistence after the withdrawal of p.o. treatment,
(3-30 days after injections)

HYPERTERMIA; EPS (rigidity, dysartria, dysforia, tremor),

VEGETATIVE SY. (tachycardia, ↑ BP, tachypnoe, urinary incontinence);

DISORDERS OF BEHAVIOUR & CONSCIOUSNESS (delirium, somnolence, comma, epileptic paroxysms);

leukocytosis, homeostatic disturbance, ↑hemocoagulation ….

ANTIPSYCHOTICS (neuroleptics) ... cont.

Atypical (II. generation)

(*without EPS, tardive dyskinesia, prolactinemia, malignant neuroleptic syndrom*)

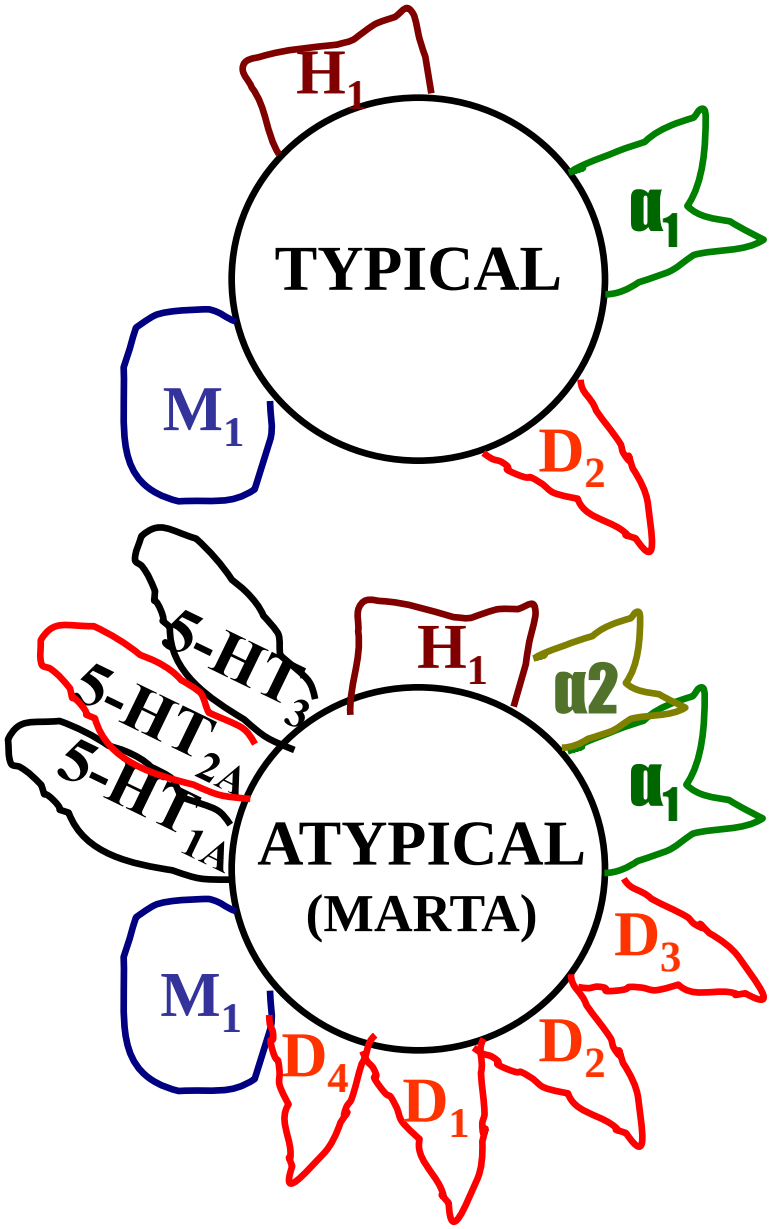
- **MARTA** *(Multi-Acting Receptor Targeted Agents)*
  clozapine, olanzapine, quetiapine

- **SDA** *(Serotonin-Dopamine Antagonist)*
  risperidone, ziprasidone, sertindole

- **D2/D3 antagonists**
  sulpiride, amisulpride

- **DSSS** *(Dopamine-Serotonin System Stabilizers)*
  aripiprazole

ANTIPSYCHOTICS



D_2 blockade = antipsychotic effects

M_1 blockade = dry mouth, diplopia, constipation

α_1 blockade = ↓ BP, dizziness

H_1 blockade = drowsiness, weight gain

More selective for mesolimbic pathways

↓

less EPS

<u>therapeutic efects</u>	<u>side effects</u>
$D_{1,2,3,4}$	α_1, α_2, M_1, H_1
$5\text{-}HT_{2A}$	

Stephen M. Stahl, 2000

ANTIPSYCHOTICS (neuroleptics) ... cont.

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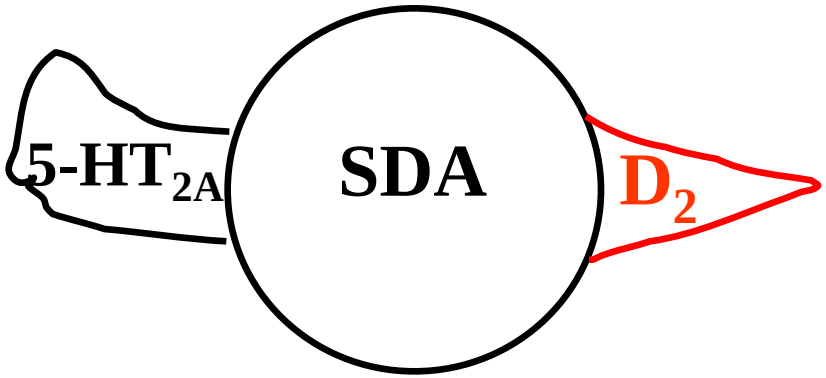
SDA (Serotonin-Dopamin Antagonist)

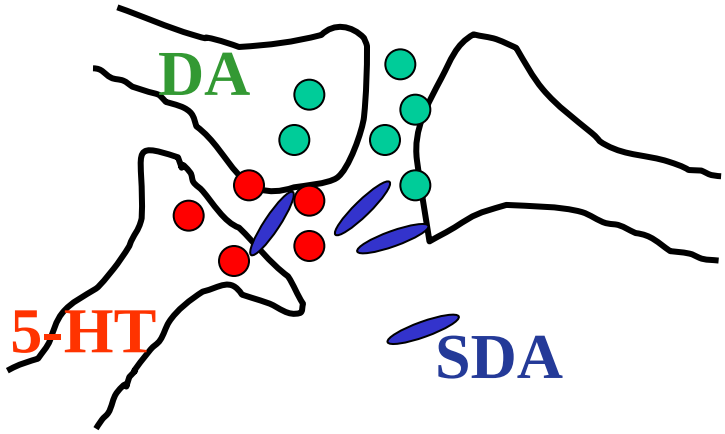


risperidone, olanzapine, sertindol, seroquel

↓

better effect on negative symptoms,
less of EPS (especially at lower dosage)

5-HT → inhibition of DA realease

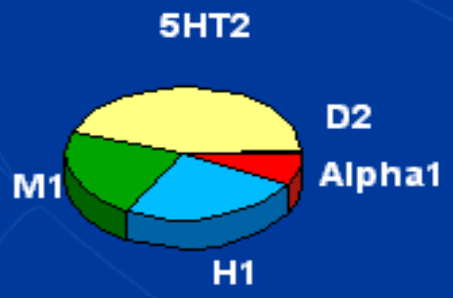


5-HT r. blockade → ↑ release of DA
= suppression of
impact of D_2 blockade

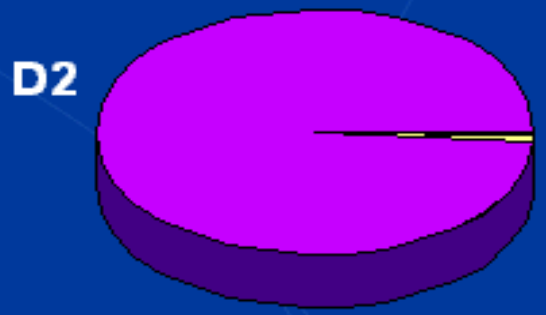
Stephen M. Stahl, 2000

ANTIPSYCHOTIC RECEPTOR BINDING

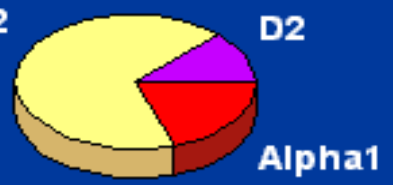
clozapine



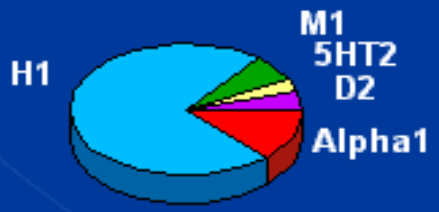
amisulpride



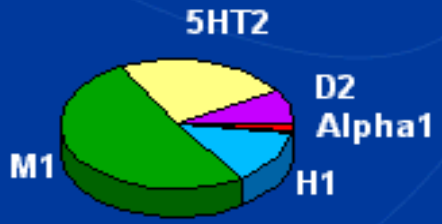
risperidone



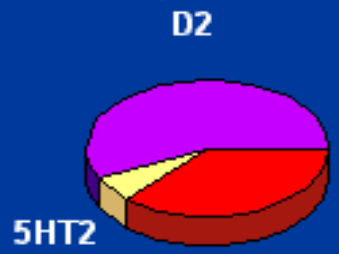
quetiapine



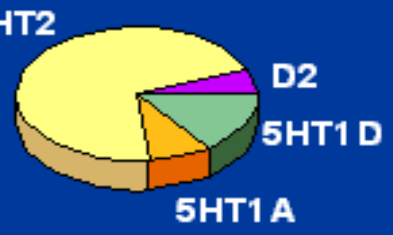
olanzapine



haloperidol



ziprasidone



From Richelson 1996; Schoemaker et al 1997; Seeger et al 1995

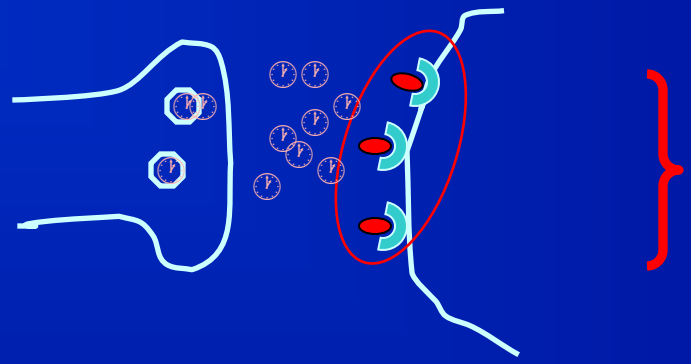
Comparative Side Effect Profiles of the New Antipsychotics

	clozapine	risperidone	olanzapine	amisulpride	quetiapine	ziprasidone
Sedation	++	+	++	+/-	+	+
EPS	-	+	+	+	(+)	+
Orthostatic hypotension	++	+	(+)	-	+	+
Weight gain	++	+ (+)	+ +	+	+ (+)	(+)
Prolactin increase	(+)	++	(+)	++	(+)	+
Salivation/dry mouth	+	(+)	+	-	(+)	(+)
Haematological effects	++	(+)	+	(+)	(+)	(+)

+ mild ++ moderate

D2/D3 antagonists

in psychosis

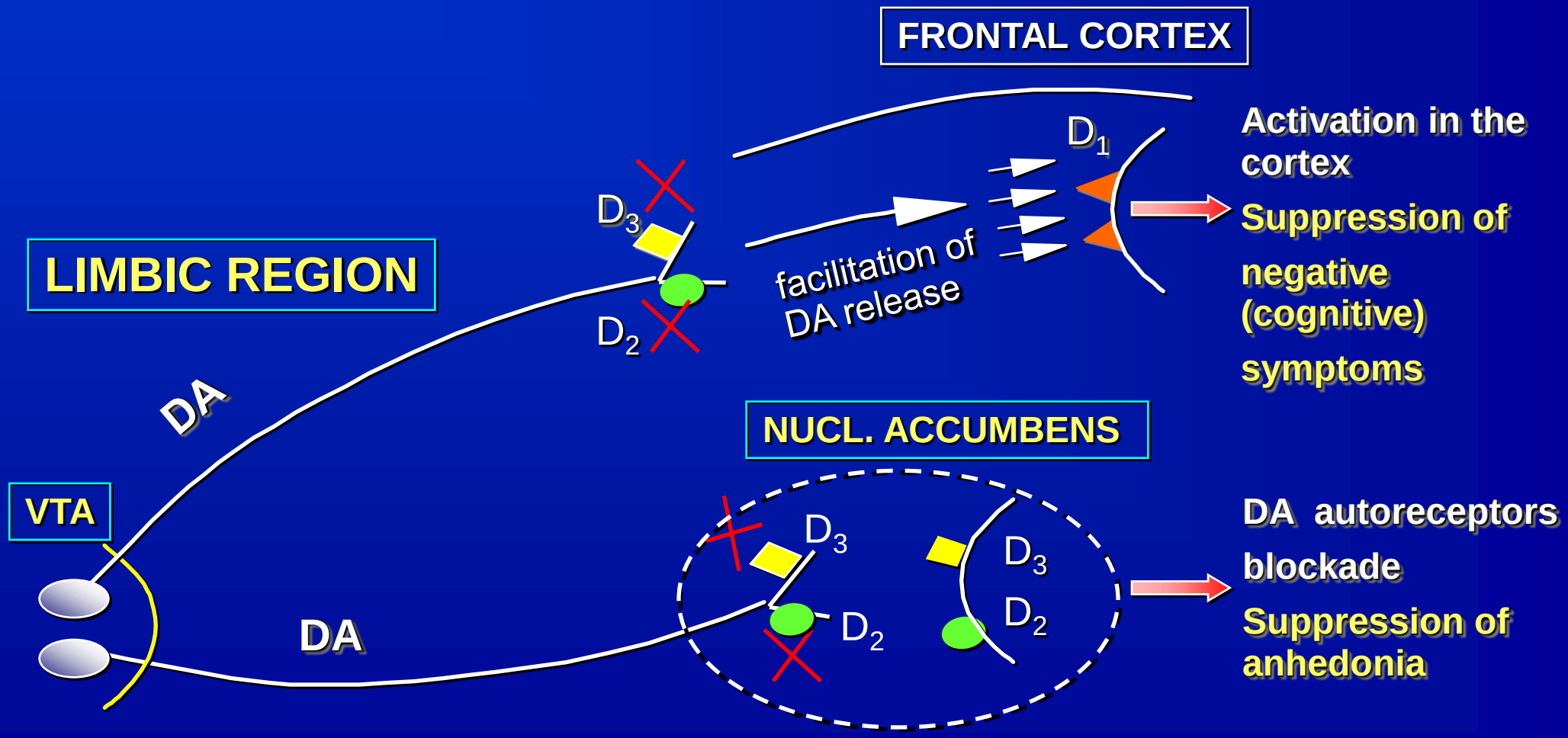


SUPPRESSION OF POSITIVE SYMPTOMS

blockade of $D_{2,3}$ postsynaptic receptors

D2/D3 antagonists

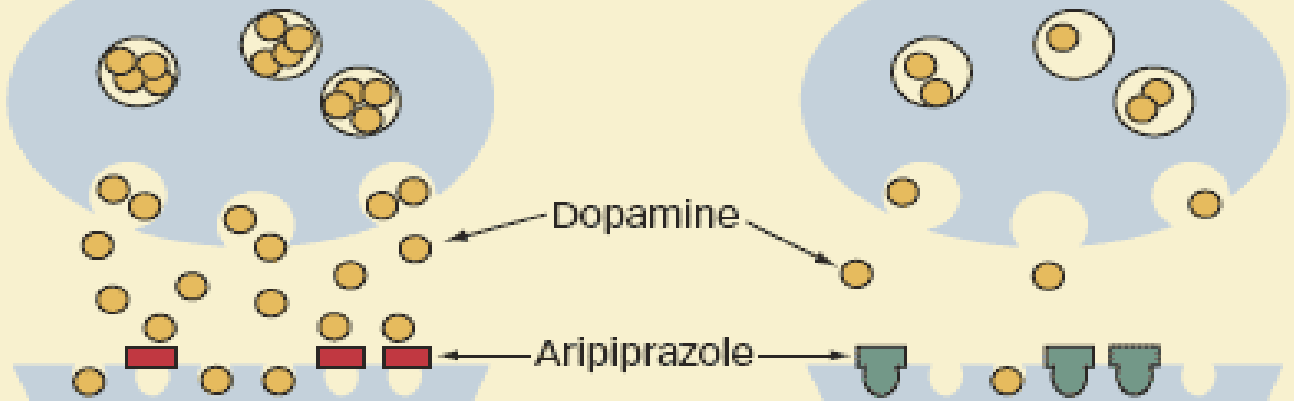
Selective blockade of D_3/D_2 autoreceptors in the limbic region



Aripiprazole → partial agonist of D2 receptors

blocks D2 receptors in regions with high DAergic activity

stimulates D2 receptors in regions with low DAergic activity



aripiprazol "normalizes" dopaminergic activity

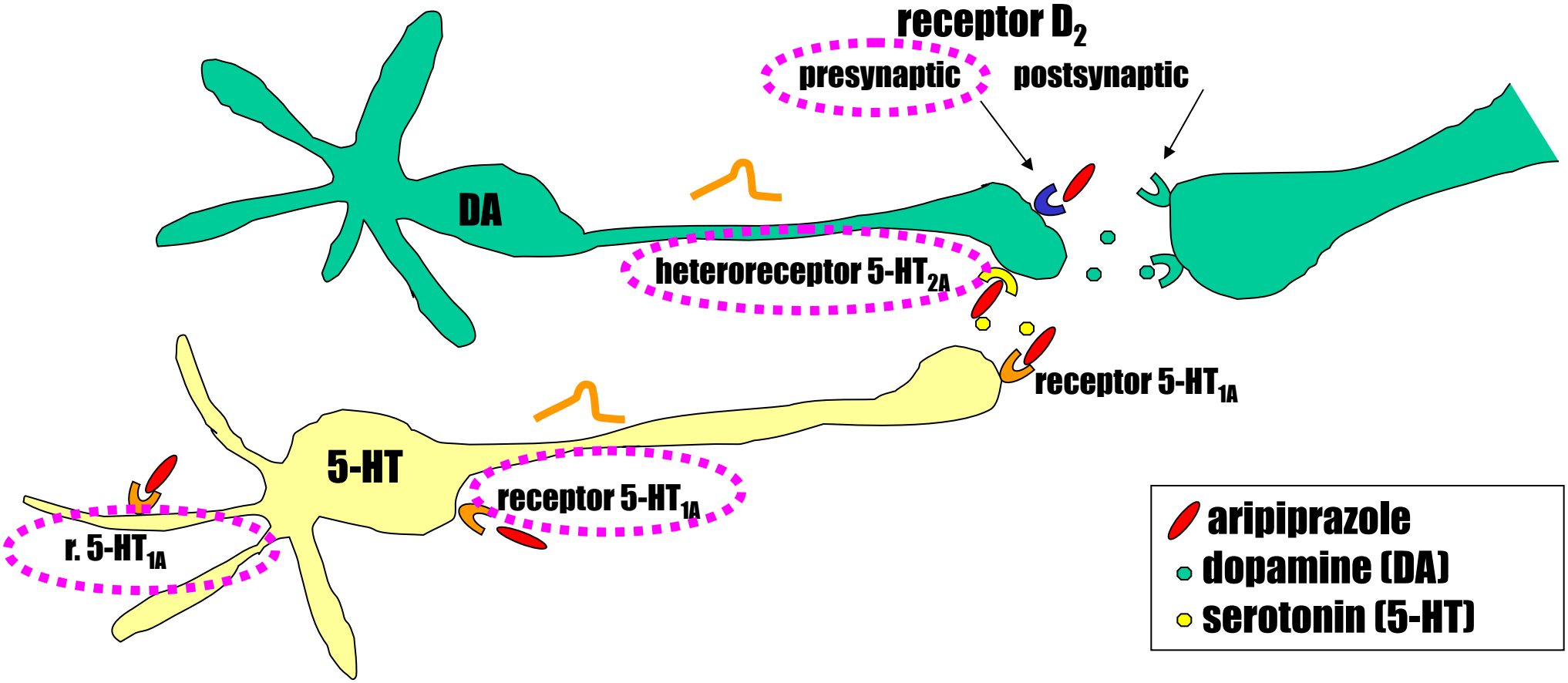
Ozdemir et al., 2002

DSSS *(Dopamine-Serotonin System Stabilizers)*

ARIPIPRAZOLE suggested mechanisms of action:

- partial agonist at D_2 autoreceptors and $5\text{-}HT_{1A}$ somatodendritic receptors
- antagonist at $5\text{-}HT_{2A}$ heteroreceptors of dopaminergic neurons

(Burris at al., 2002; Jordan et al., 2002)



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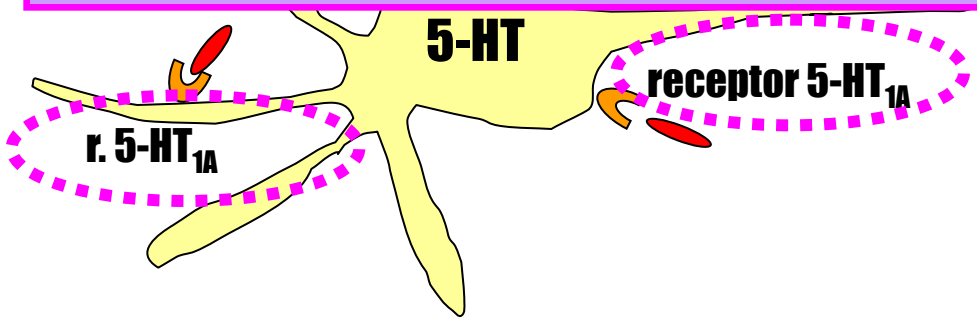
(Burris at al., 2002; Jordan et al., 2002)

- partial agonist at D2 autoreceptors → inbibition of DA release

- partial agonist at 5-HT1A somatodendritic receptors
  → augmentation of serotonin transmission (antianxiety, antidepressant effects)
  → inbibition of DA release



aripiprazole
dopamine (DA)
serotonin (5-HT)

DSSS *(Dopamine-Serotonin System Stabilizers)*

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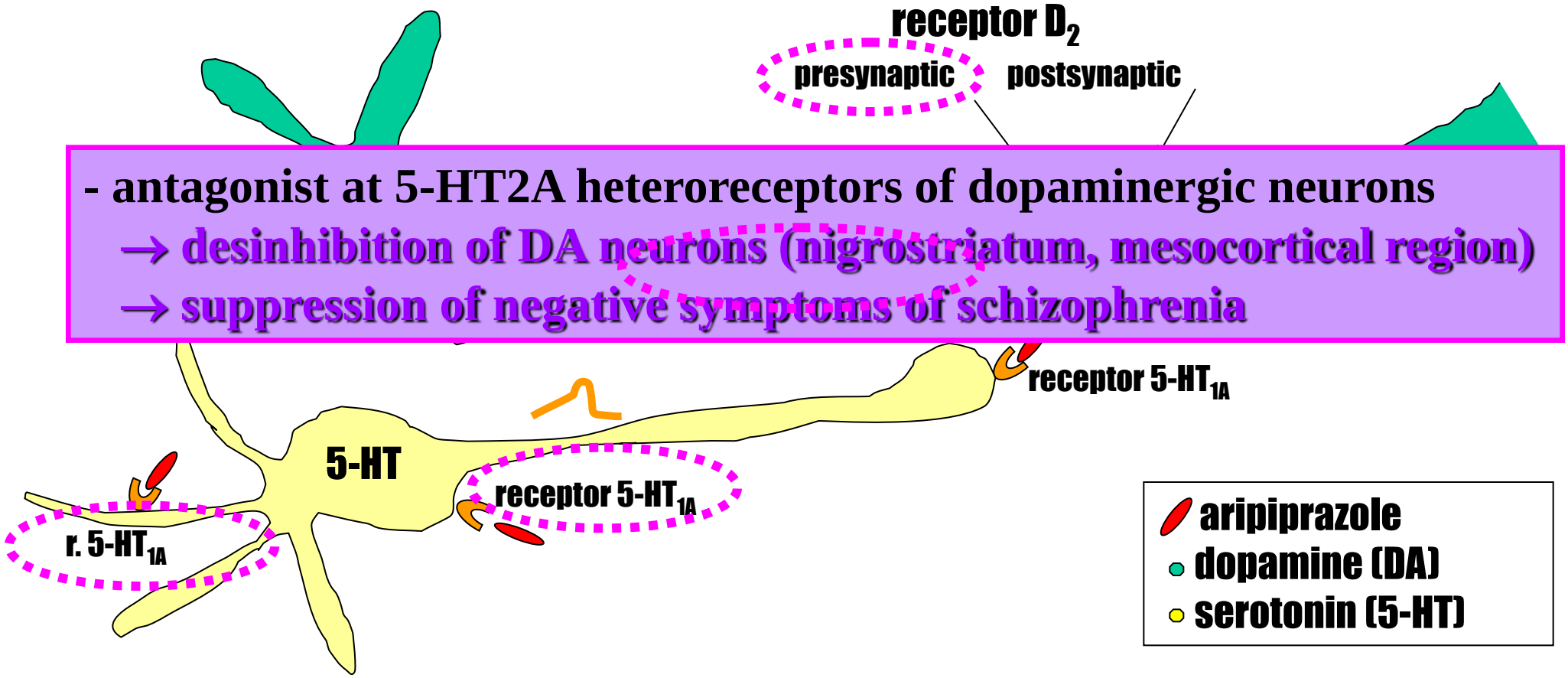


ARIPIPRAZOLE - main indications:

1. Schizophrenia in adults and adolescents (age 13-17)

2. Acute manic or mixed episodes of bipolar disorder I. (as monotherapy or with valproate in adults or adolescents of age 10-17)

3. Adjunctive therapy in major depression

4. Irritability associated with autistic disorder in pediatric patients (age 6-17)

5. Acute agitation associated with schizophrenia or bipolar disorder (intramuscularly)

Kantrowitz J.T., Citrome L. From MedscapeCME Psychiatry & Mental Health Antipsychotics A-Z, 2010, www.medscape.org/viewarticle/718207

INDICATIONS FOR ANTIPSYCHOTICS

- psychoses

- nausea, vomitus
- sleeping disorders
- anxiety

- Huntington disease
- Tourett's syndrome
- anesthesiology / neuroleptanalgesia

Antipsychotic Drugs: Side effects

SEDATION Greater with CLOZAPINE, OLANZAPINE, QUETIAPINE

HEADACHE

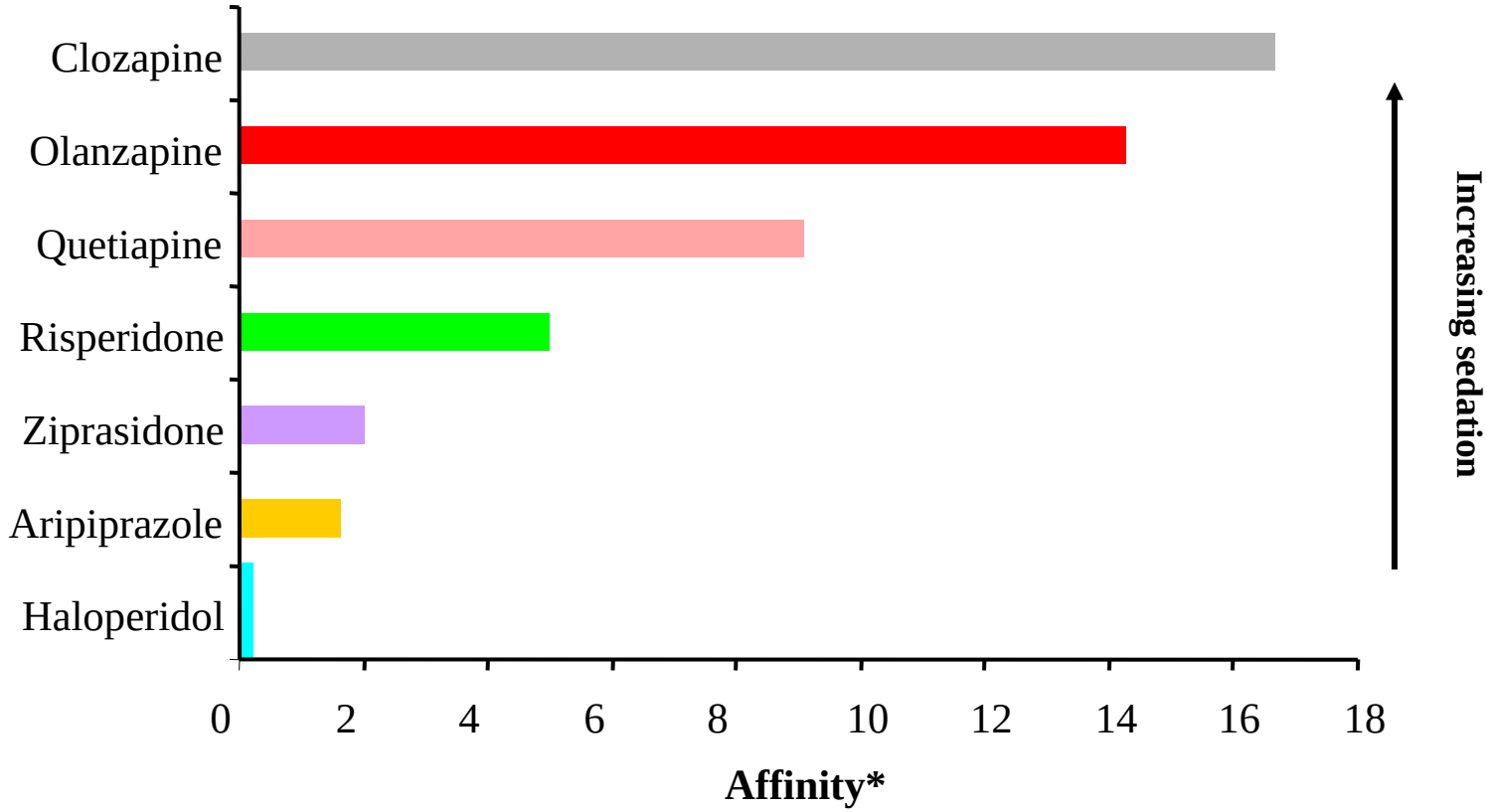
SUBJECTIVE BURDEN

- Loss of energy/drive Greater with classic
- Dysphoria Greater with classic
- Problems with memory and concentration

SLEEP DISTURBANCE

- Night sleep pattern
- Difficulty waking/daytime sleepiness
- Insomnia Greater with ARIPIPRAZOLE

Sedation may be Related to Affinity of Medications for the Histamine H1 Receptor



*Presented at 10^2 × 1/Ki (nM)
**Data with cloned human receptors

Bymaster FP *et al*. *Neuropsychopharmacology* 1996;14:87–96;

Antipsychotic Drugs: Side effects

CARDIOVASCULAR

- Palpitations/tachycardia ? Greater with QUETIAPINE
- Postural hypotension Greater with CLOZAPINE, LEVOMEPROMAZINE
- ECG abnormalities
  - QT prolongation Greater with SERTINDOLE, ZIPRASIDONE

GASTROINTESTINAL

- Nausea/vomiting, constipation, diarrhoea

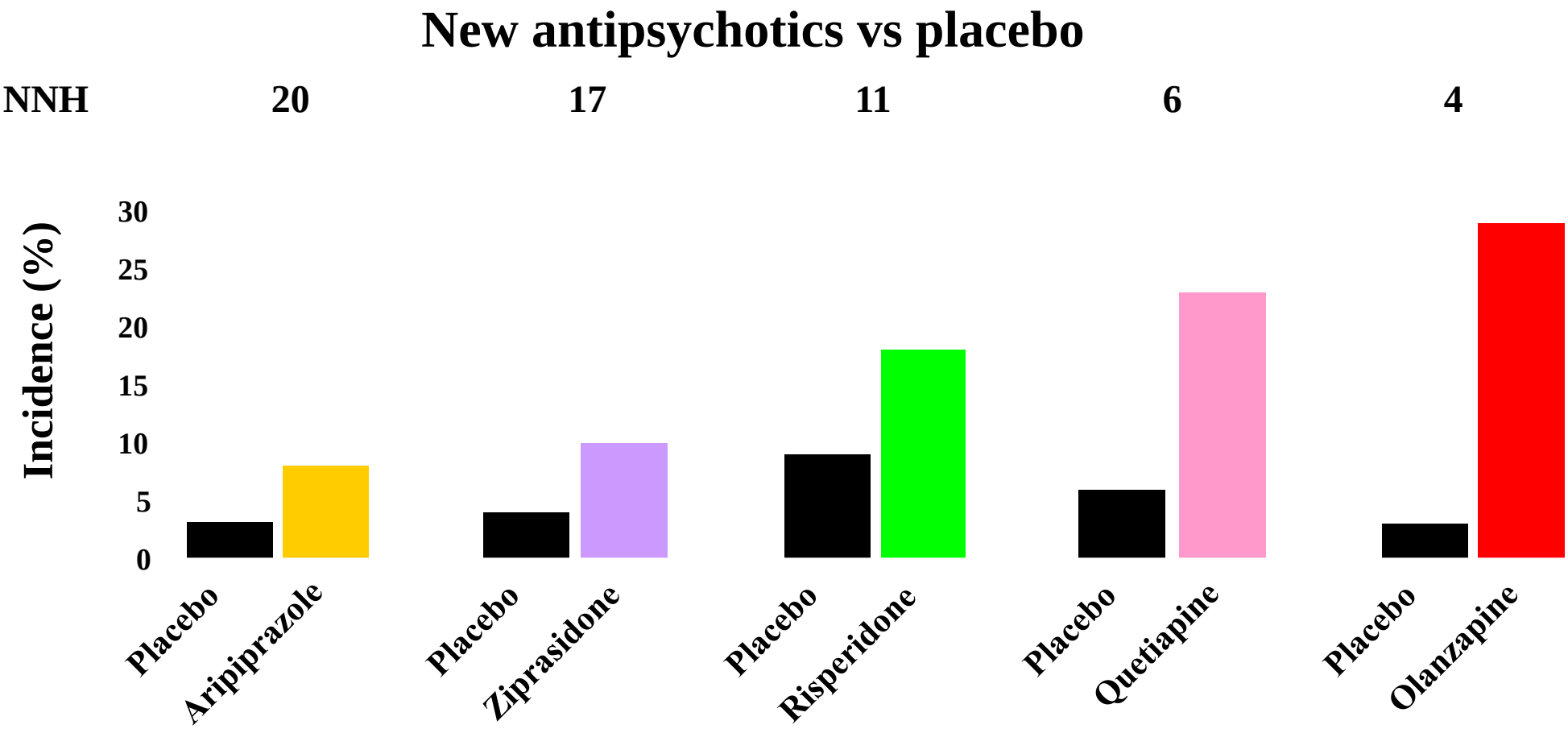
ENDOCRINE

- Weight gain Greater with CLOZAPINE and OLANZAPINE
- Diabetes Greater with CLOZAPINE and OLANZAPINE
- Decreased T3 Greater with QUETIAPINE

HEPATIC DYSFUNCTION

- Increased transaminases ? Greater with OLANZAPINE
- Cholestatic jaundice

Clinically Significant Weight Gain (≥7%)



NNH = number needed to harm

Abilify® (aripiprazole) US PI, October 2006. Geodon® (ziprazidone) US PI, August 2004. Risperdal® (risperidone) US PI, November 2006. Seroquel® (quetiapine fumarate) US PI, July 2007. Zyprexa® (olanzapine) US PI, March 2002.

Antipsychotic Drugs: Side effects

HYPERSALIVATION Greater with CLOZAPINE

ANTICHOLINERGIC EFFECTS

- Dry mouth / Blurred vision / Urinary hesitancy

NOCTURNAL ENURESIS Greater with RISPERIDONE

SEXUAL SIDE-EFFECTS Greater with RISPERIDONE, AMISULPRIDE

- Loss of libido
- Females: Anorgasmia/Change in menstruation
- Males: Erectile dysfunction/Ejaculatory disturbance

  ? Reduced ejaculatory volume with SERTINDOLE

PROLACTIN ELEVATION Dose-related with RISPERIDONE, AMISULPRIDE

Antipsychotic Drugs: Side effects

CNS

- Emergence of disorientation/clouding of consciousness
- Seizures Greater with CLOZAPINE,? Classic antipsychotics
- Neuroleptic malignant syndrome Classic

OPHTHALMOLOGICAL

- Glaucoma
- Corneo-lenticular opacities/pigmentary lesions

CUTANEOUS REACTIONS

- Photosensitive skin rash
- Pigmentation

HAEMATOLOGICAL

- Blood dyscrasias Greater with CLOZAPINE

ANTIPSYCHOTIC-INDUCED MOVEMENT DISORDER

Early onset

Parkinsonism (Classic potent D2)

Acute akathisia (Classic, aripiprazole)

Acute dystonia (Classic potent D2, risperidone dose dependant)

Late onset

Chronic akathisia ?

Tardive dystonia ?

Tardive dyskinesia (Classic)

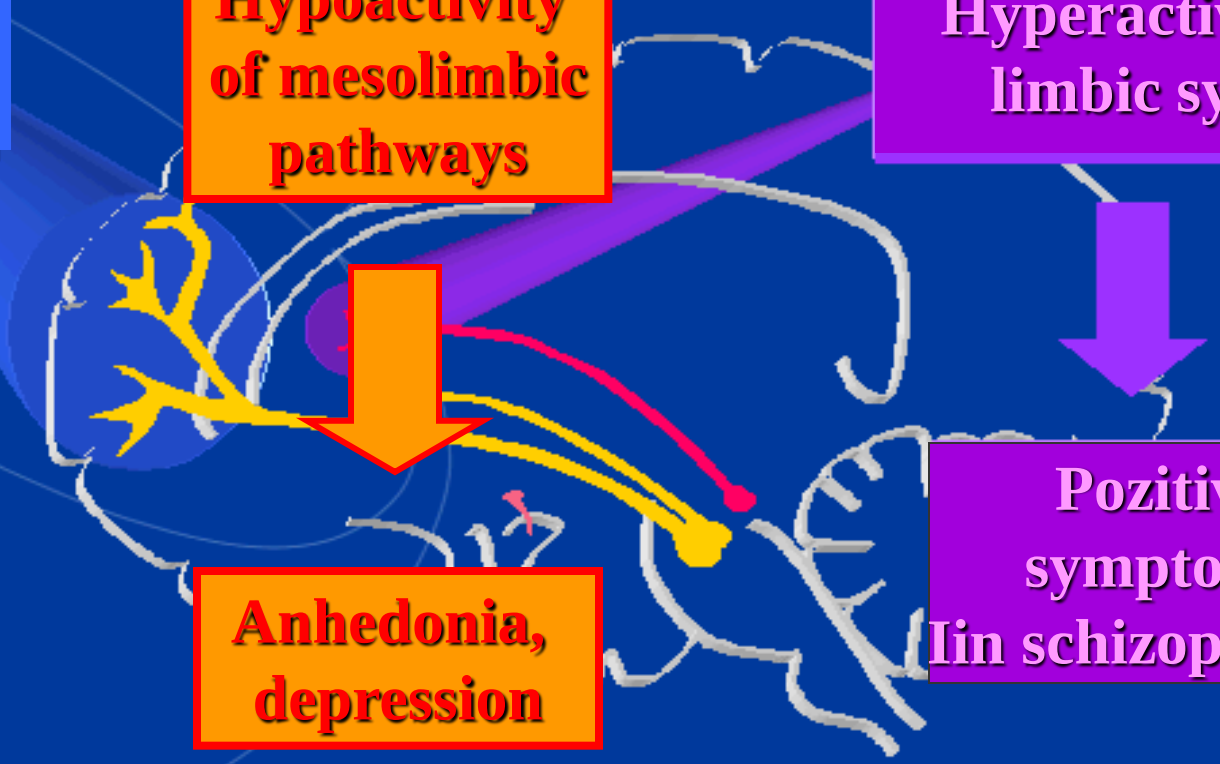
The Dopamine Hypothesis of Schizophrenia

Mesofrontal and Mesolimbic Dopamine Pathways

Hypoactivity in frontal. cortex

Hypoactivity of mesolimbic pathways

Hyperactivity of limbic sytem



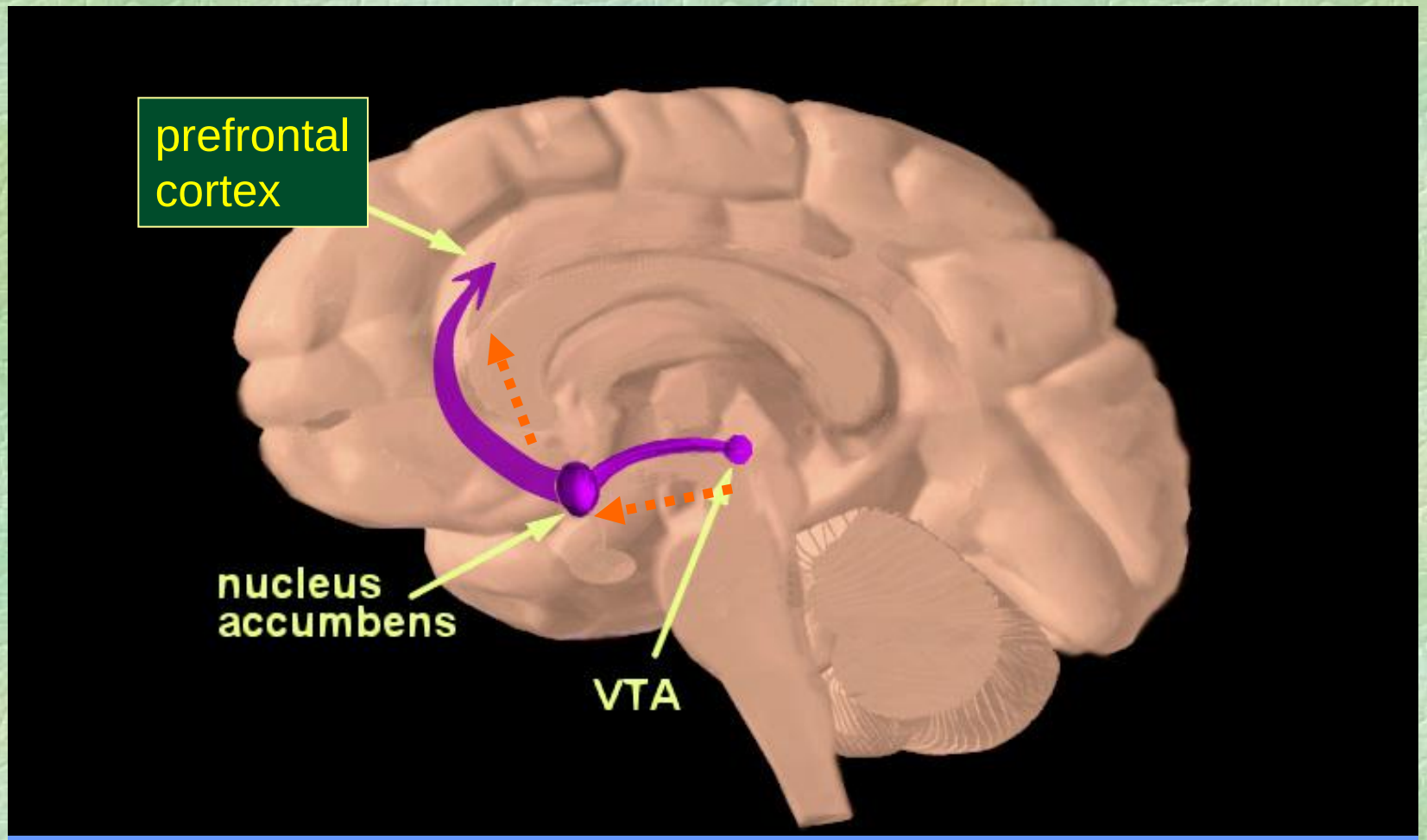
Negative symptoms in schizofrenia

Anhedonia, depression

Pozitive symptoms Iin schizophrenia

Dopaminergic "reward pathway"
- activation (food, sex, drug of abuse …) ⇒ **EUPHORIA**

In case of hypoactvity ⇒ ANHEDONIA, DEPRESSION



Serotonin (5-HT)

synthesis tryptophan → hydroxylase ⇒ 5-hydroxytryptophan →
decarboxylase ⇒ 5-hydroxytryptamine (5-HT)

storage - in vesicles (with ATP) in presynaptic terminals
- in a mobile extravesicular cytoplasmic pool

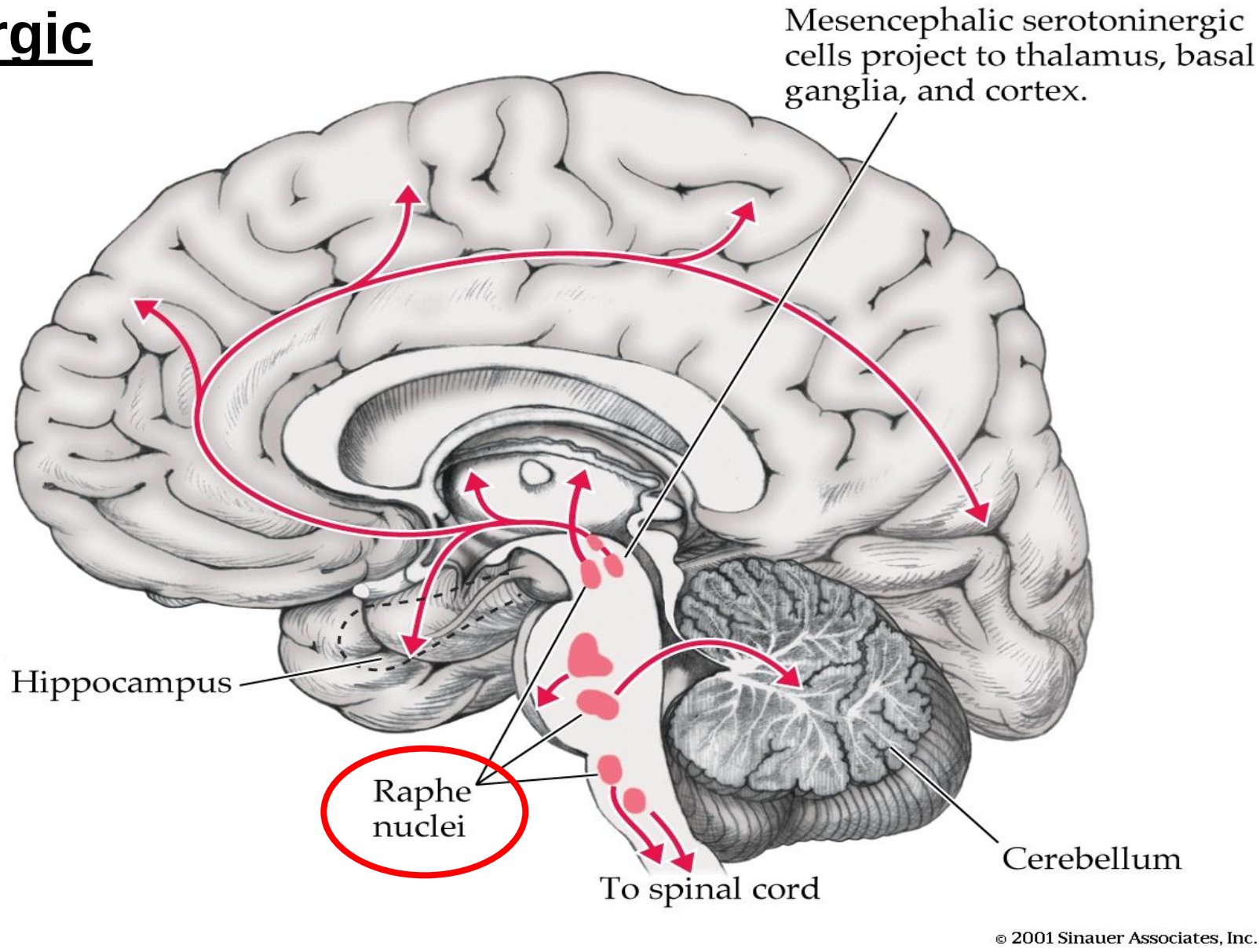
breakdown - re-uptake ! !
- MAO_A (cytoplasmic)

receptors $5\text{-}HT_{1A, B, C, D}$ - ↓ cAMP
$5\text{-}HT_{2A, B, C}$ - stimulation of phosphoinositol metabolism
$5\text{-}HT_{4}$ - ↑ cAMP
$5\text{-}HT_{5A, B}$
$5\text{-}HT_{6, 7}$

= metabotropic receptors

$5\text{-}HT_{3}$ - stimulation of ion channels (= ionotropic receptor)

Serotonergic pathways



Serotonin (5-HT)

Serotonin = neurotransmitter: 1954, John Welsh (UK)

synthesis tryptophan → hydroxylase ⇒ 5-hydroxytryptophan → decarboxylase ⇒ 5-hydroxytryptamine (5-HT)

storage - in vesicules (with ATP)
- in cytoplasma

breakdown - re-uptake !
- MAO_A (in cytoplasma)

receptors $5\text{-}HT_{1A, B, D, E, F}$
$5\text{-}HT_{2A, B, C}$
$5\text{-}HT_4$ $5\text{-}HT_{5A, B}$
$5\text{-}HT_{6, 7}$

= metabotropic receptors

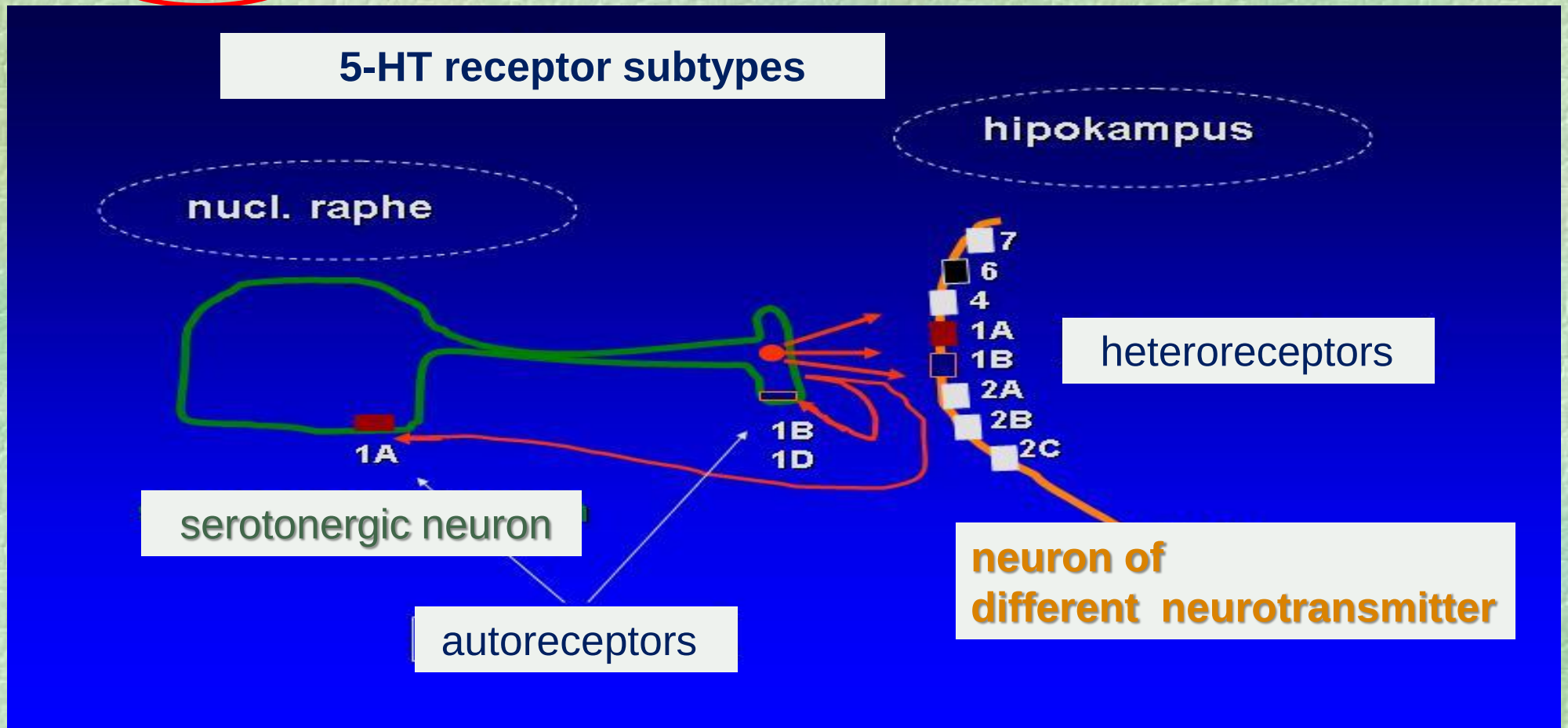
$5\text{-}HT_3$ - stimulation of cation channels (= ionotropic receptor)

Serotonergics

↓ 5-HT → deregulations of other neurotransmitters

Regulation of stress response
and behaviour (anxiety, depression, psychosis)

5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2B} , 5-HT_{2C} , 5-HT_{3}



ANTIDEPRESSIVE DRUGS

SSRI = Serotonin Selective Reuptake Inhibitors

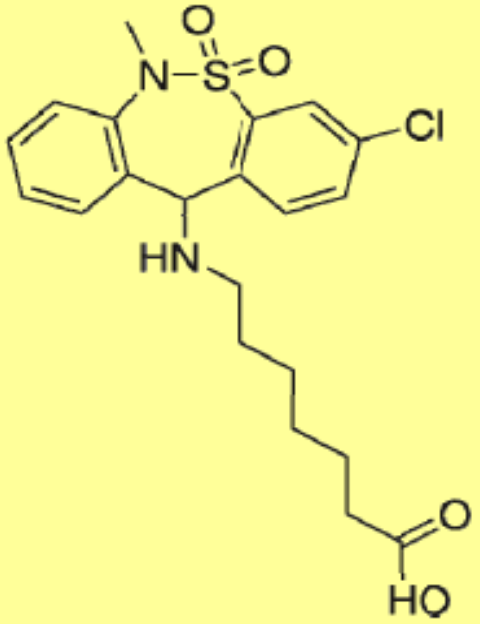
- citalopram (Citalec, Cipram, Seropram)
- fluoxetin (Prozac, Fontex, Lovan, Seronel, Fluctin)
- fluvoxamin (Luvox, Fevarin, Movox)
- sertralin (Zoloft, Lustral)
- paroxetin (Paxil, Seroxat, Aropax, Loxamil, Remood)

ANTIDEPRESSIVE DRUGS

- stimulation of 5-HT reuptake
- increase of extracellular DA concentration in nucleus accumbens

SSSE = Selective Serotonin Specific Enhancers

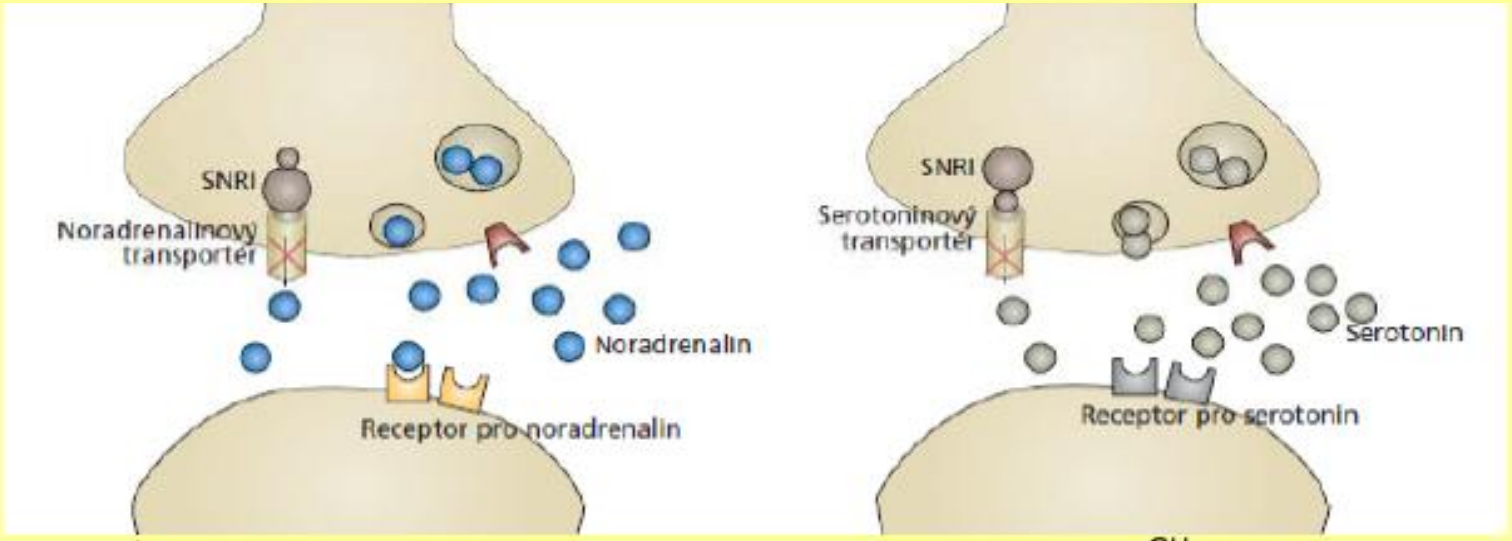
- Tianeptin (Coaxil, Tatinol, Stablon)

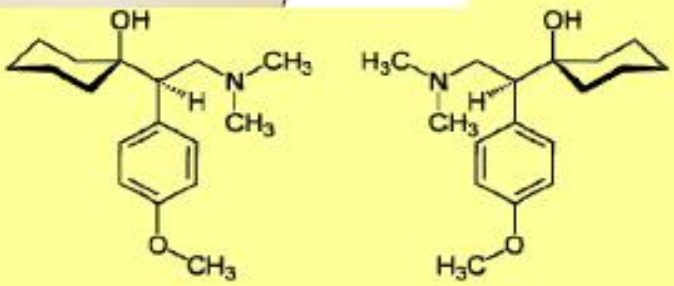


ANTIDEPRESSIVE DRUGS

SNRI = Serotonin and Norepinephrine Reuptake Inhibitors

- Venlafaxin (Argofan, Efectin), Milnacipram, Duloxetin
- *older generation – tricyclic antidepressants - Imipramin, Amitryptilin …*





Prof. MUDr. Jiří Raboch, DrSc - Farmakoterapie

GABA (gama-aminobutyric acid)

synthesis glutamic acid → → → decarboxylase ⇒ GABA

storage in neurones, in glial cells

beakdown - re-uptake
- GABA-transaminase (in neurones, in glial cells)

receptors $GABA_A$, $GABA_C$ - part of Cl^- channel structure, (postsynaptic)

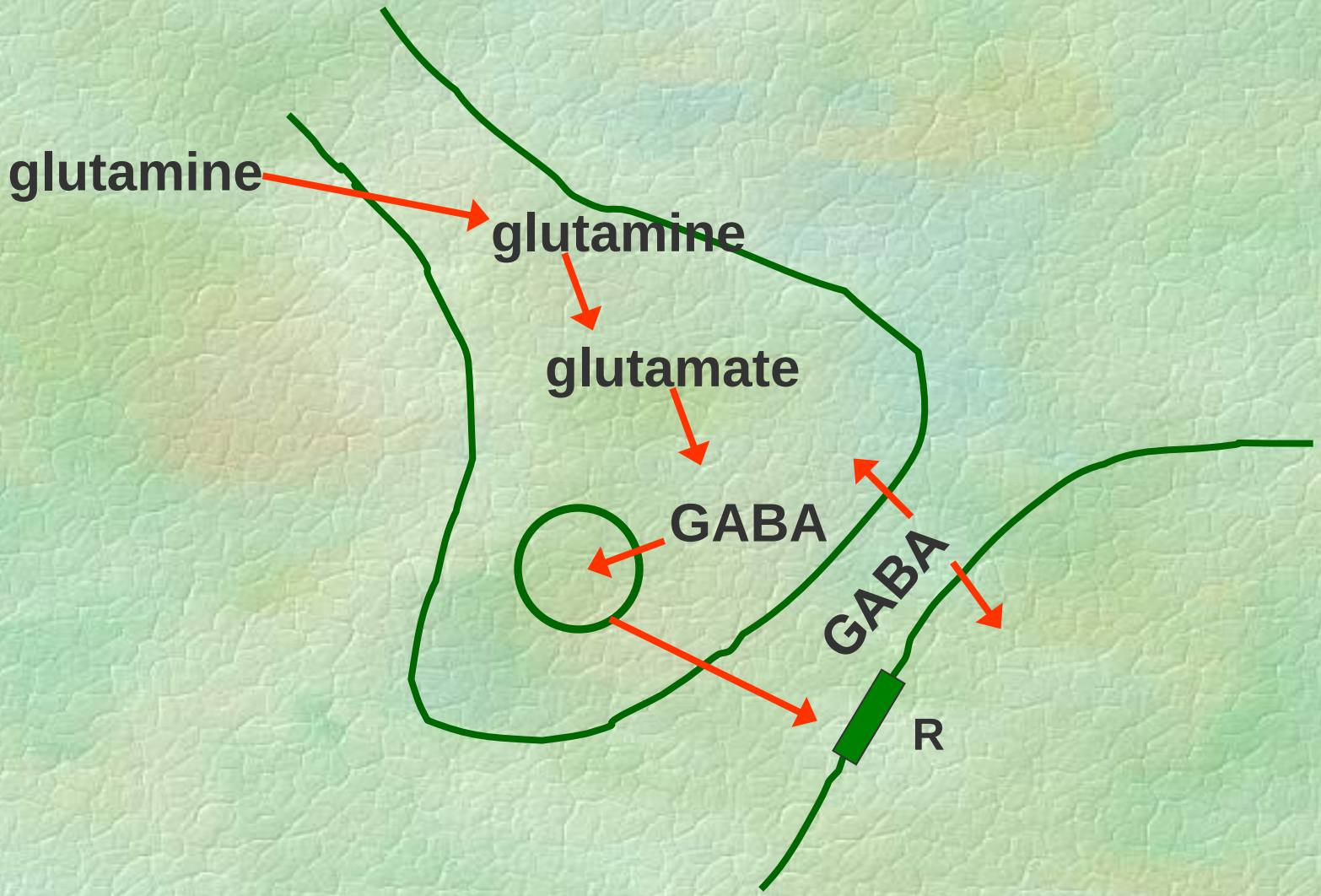
$GABA_B$ - ↓ cAMP
↑ K^+ kanálu
↓ Ca^{2+} kanálu,
(presynaptic)

GABA ↑
(sleep)

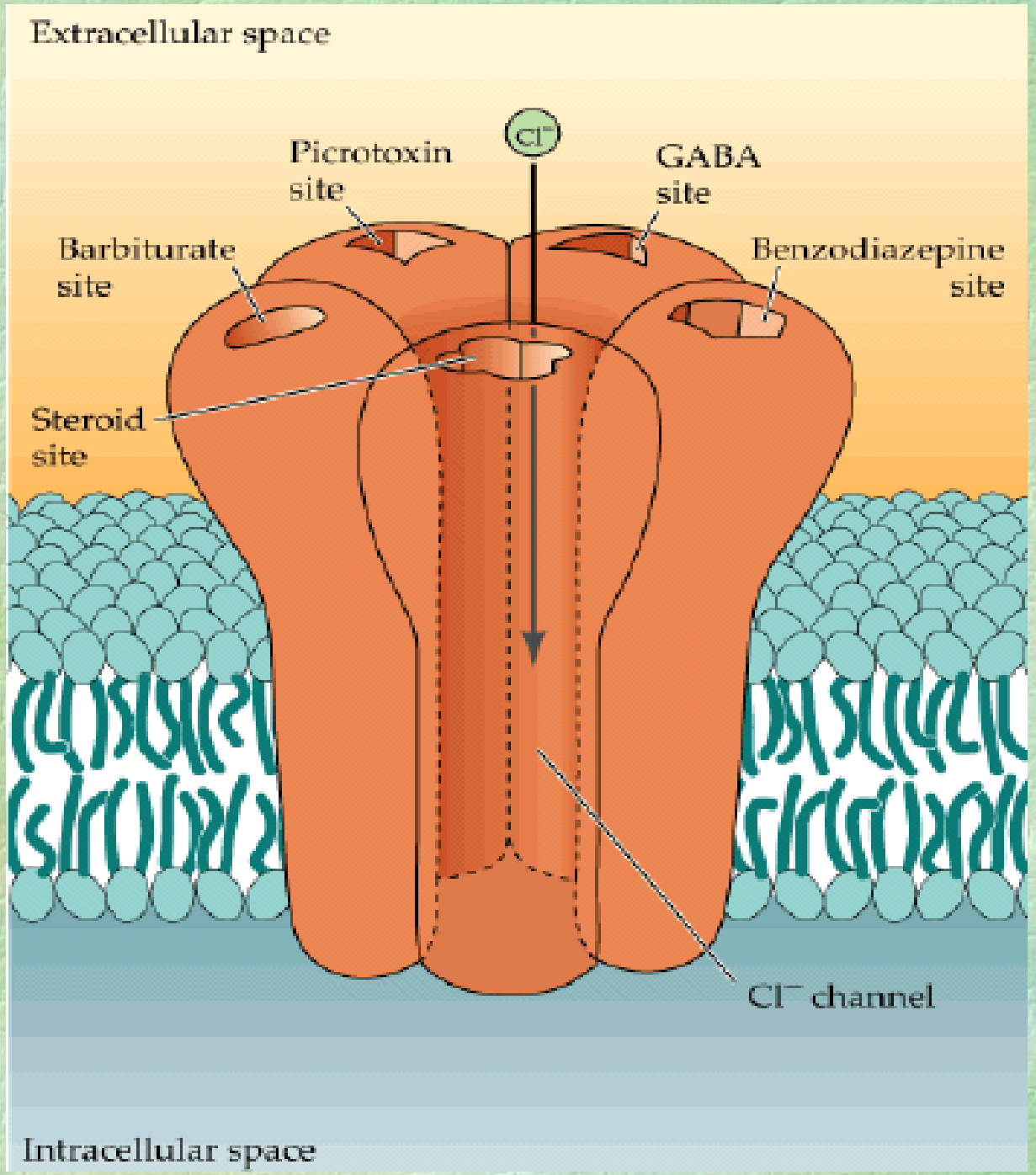
GABA ↓
(anxiety)

GABAergic synapse

gama-aminobutyric acid (GABA)



GABA receptor complex



Excitatory amino acids - glutamate, aspartate

receptors

ionotropic:

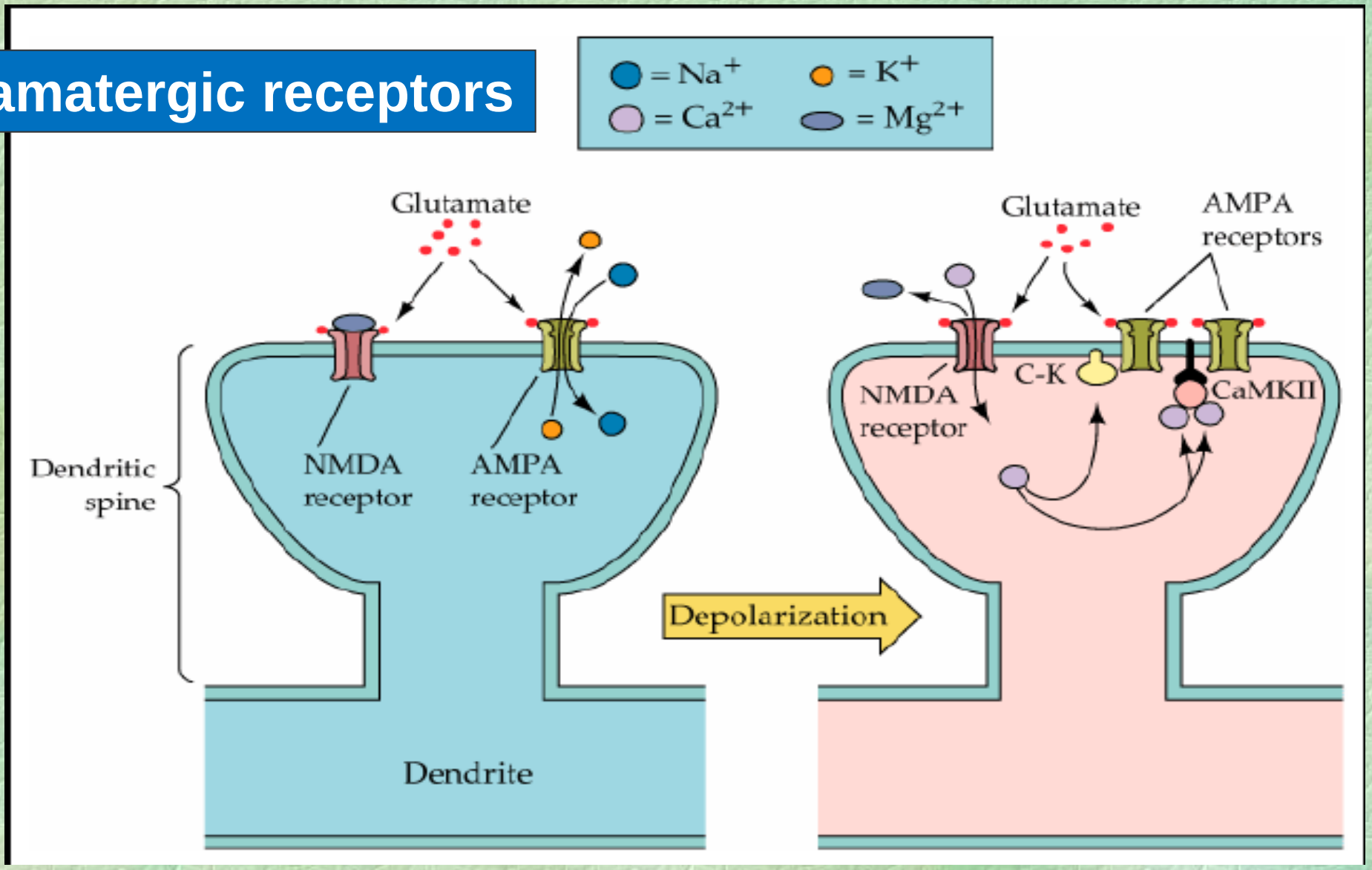
- **NMDA r (NR_{1-3}) -** (N-methyl-D-aspartate, glutamate)
- **AMPA r. ($GluR_{1-4}$)** – (alfa-amino-3-hydroxy-5- methyl-4-isoxazolepropionic acid)
- **kainate-ergic r. ($GluR_{5-7}$, KA_1, K_2)**

metabotropic, G-protein coupled:

$mGluR_{1-8}$ inhibition of glutamate release from presynaptic terminal or Increase of phosphatidylinositol turnover

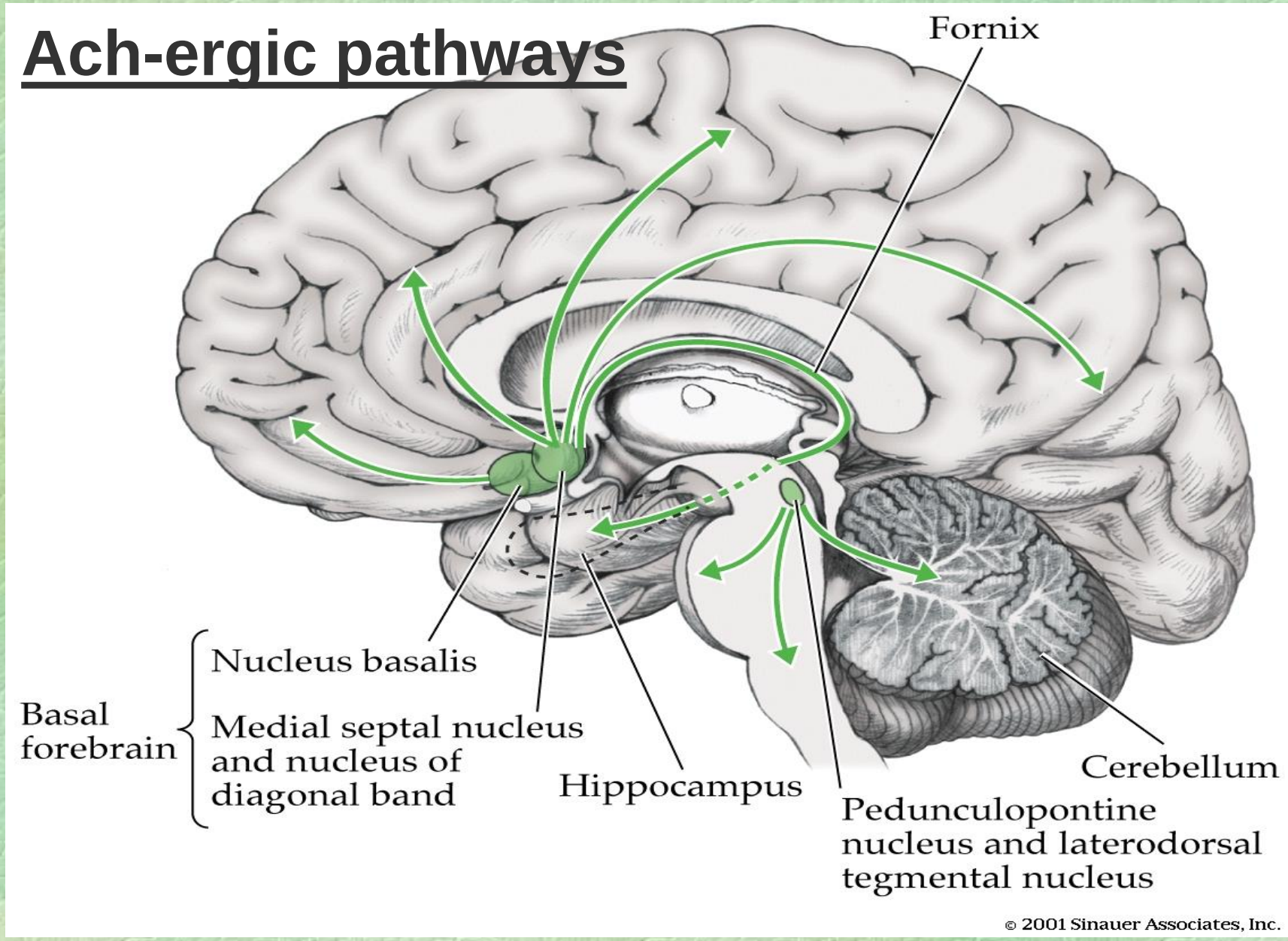
memory functions, learning processes

Glutamatergic receptors



Activation of NMDA receptors can induce changes in the activity of a larger number of AMPA receptors (LEARNING mechanismus ?)

Ach-ergic pathways



+ neuromuscular junctions

Acetylcholine

1921 – Otto Loewi (Germany) – 1936 Nobel price

synthesis choline → cholinacetyltransferase (acetyl ko-enzym A)
⇒ Ach → acetylcholinesterase ⇒ choline + acetate

storage in synaptic vesicles

breakdown (very fast)
specific cholinesterase – in neurones and neuroeffector junction

pseudocholinesterase(butyrylcholinesterase) – throughout the body, including body fluids

re-uptake choline

Acetylcholine

continuation

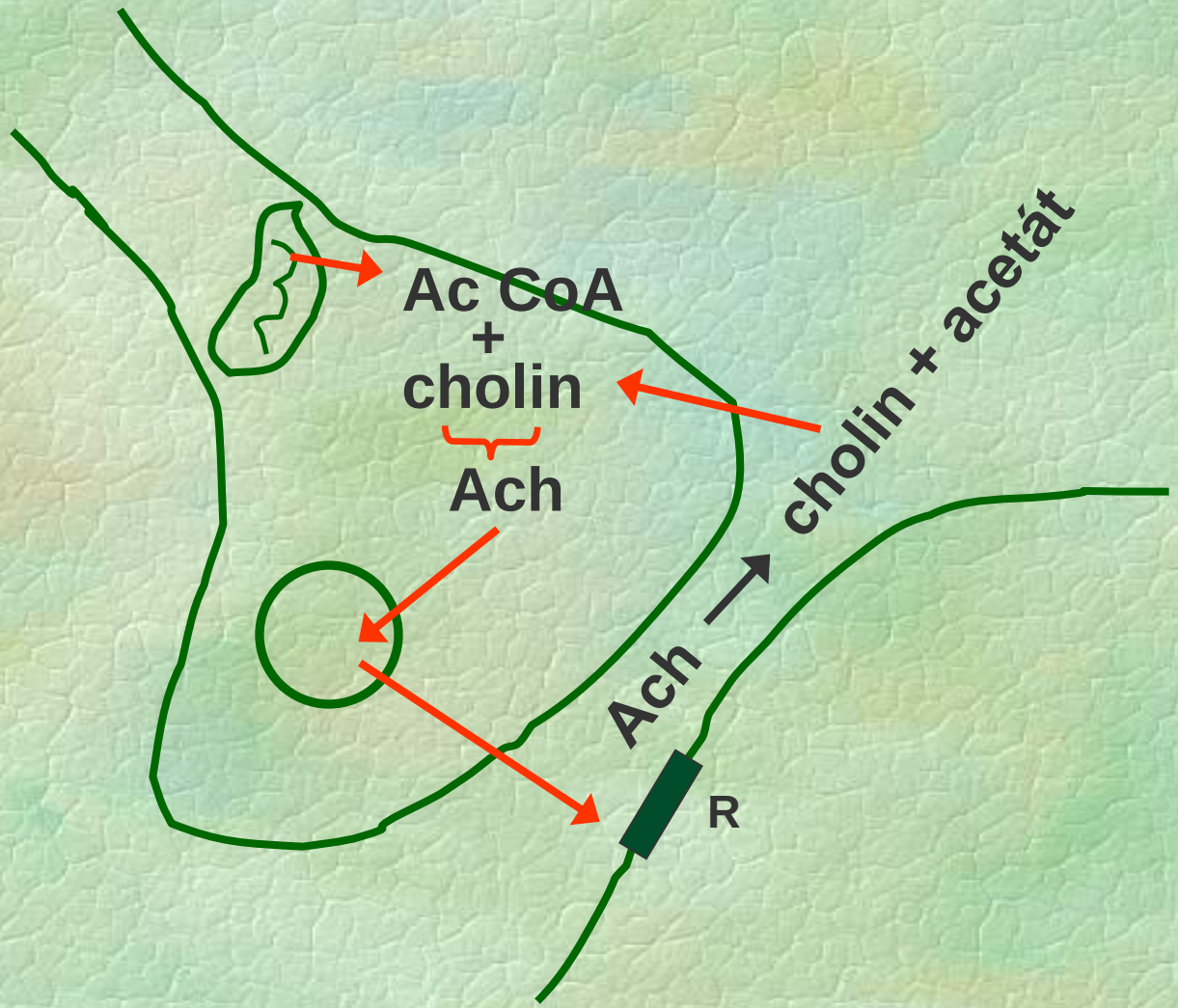
receptors M_{1-5} (muscarinic) - stimulation has slower and more sustained action, G-protein coupled

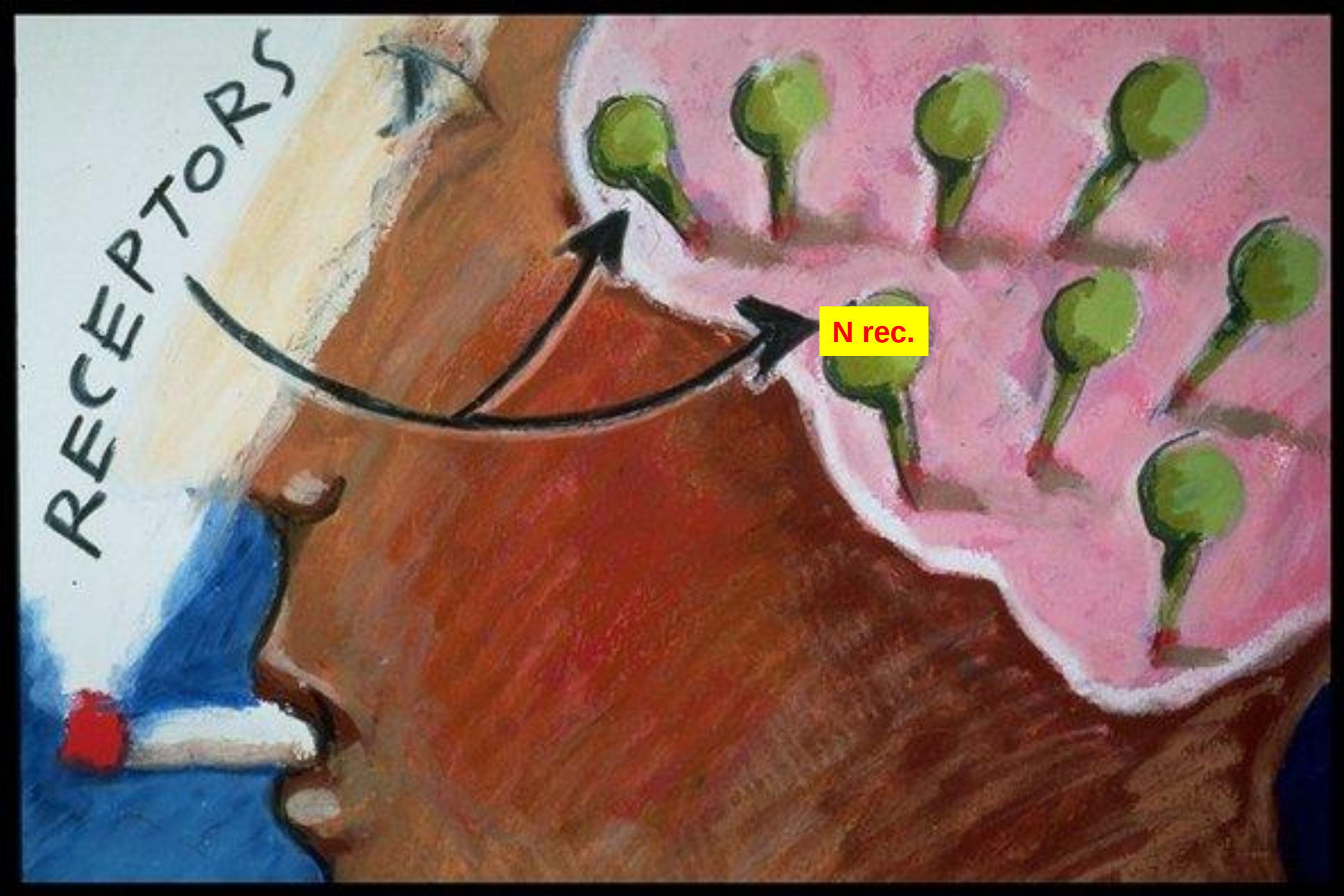
N (nicotinic) - stimulation has rapid and short action, part of receptor mediated Cl^- channels , often occurring as heteroreceptors (increase of neurotransmitter release)

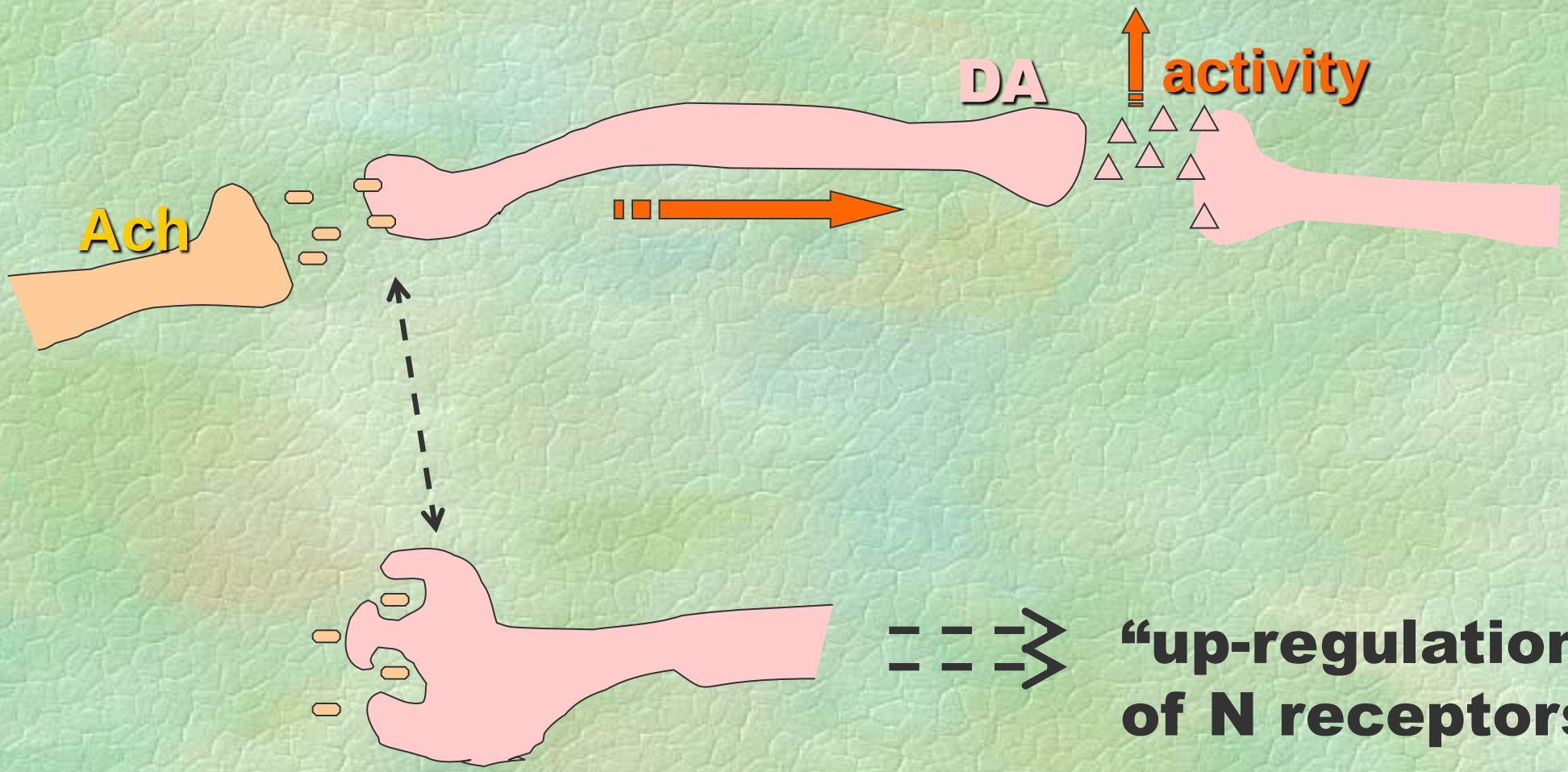
Ach ↑ IQ (learning, memory, attention, emotions, nociception, sleep . . .)

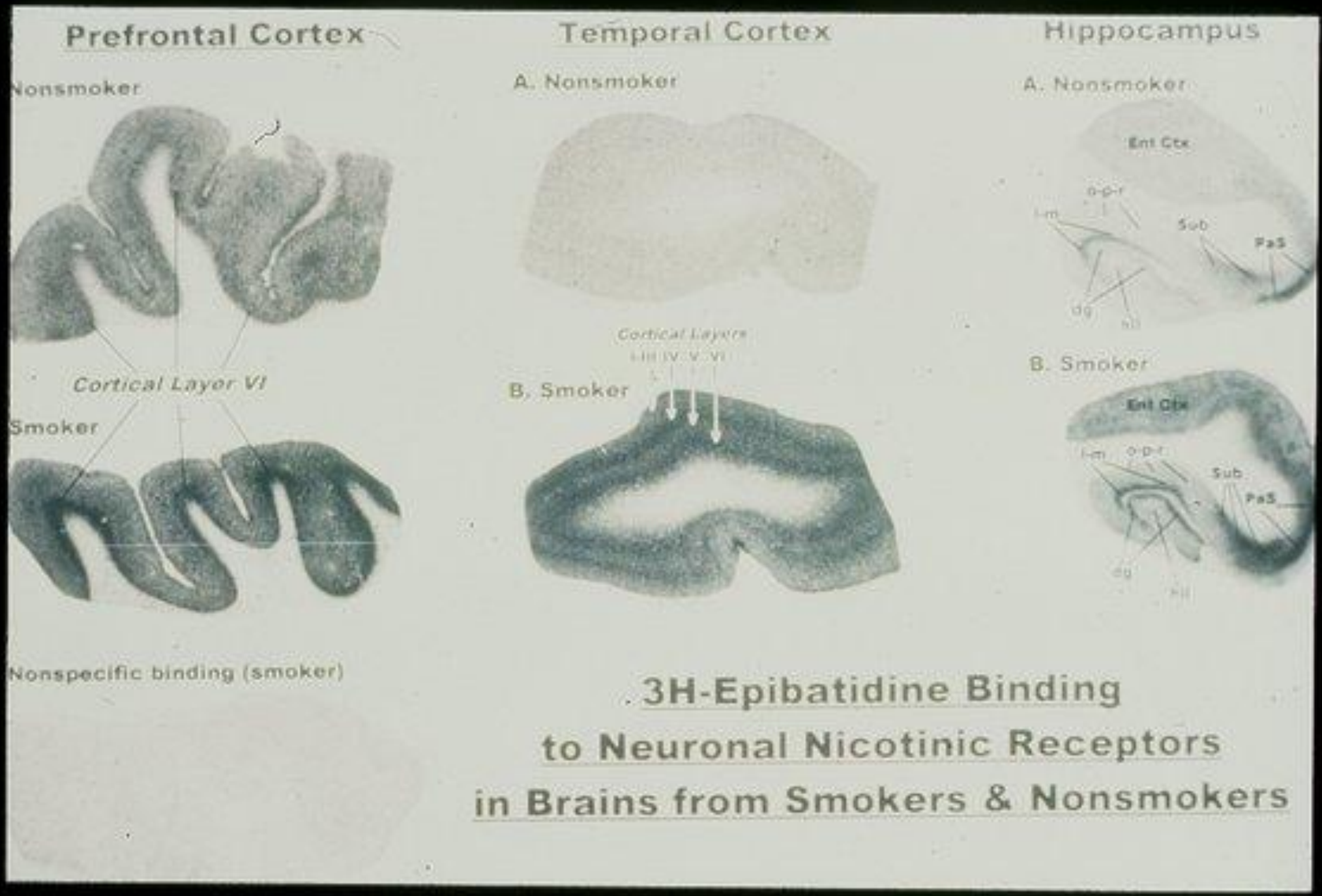
Ach ↓ demention, delirium

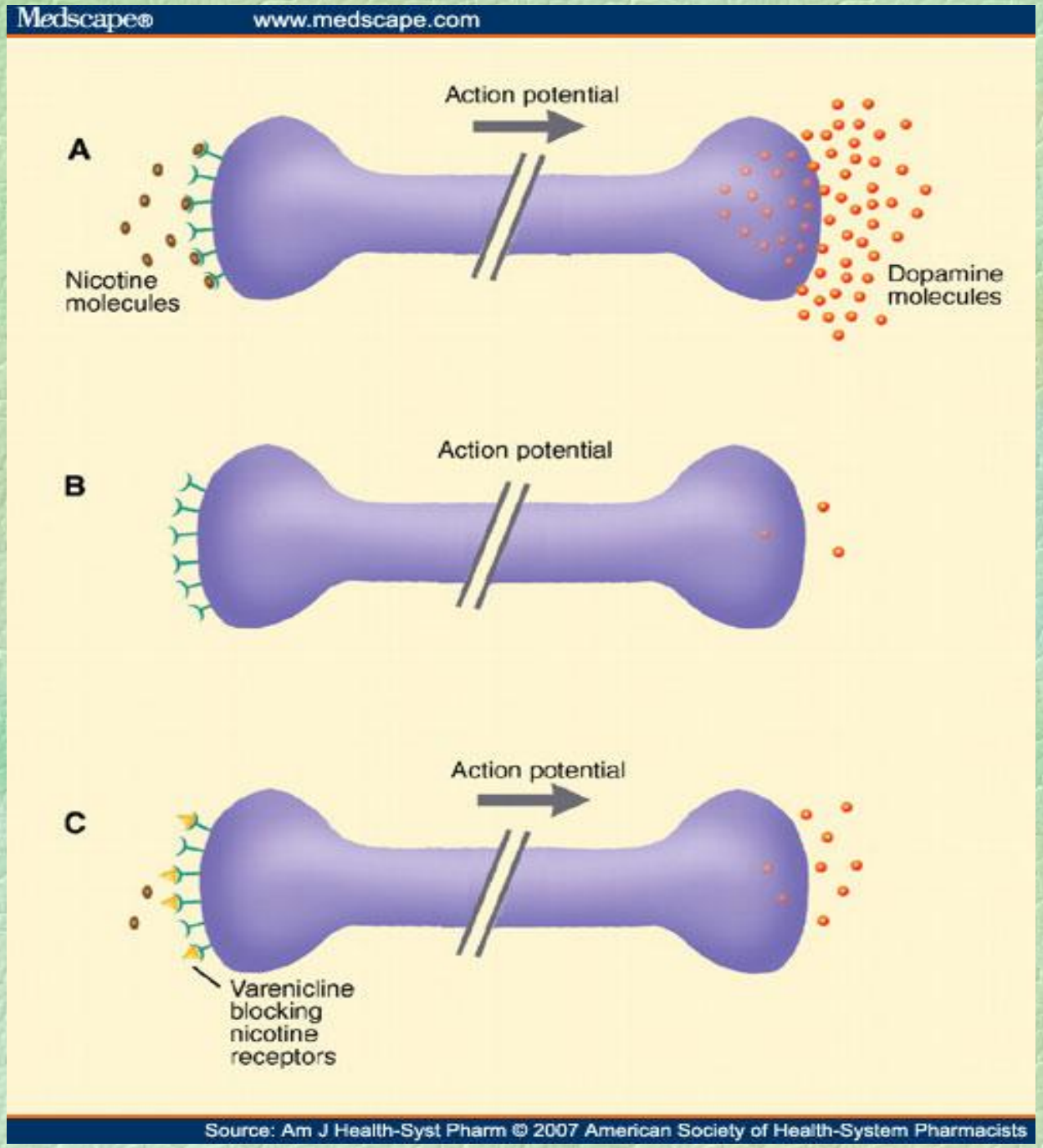
Cholinergic synapse - acetylcholin (Ach)




RECEPTORS
N rec.


DA
activity
Ach
"up-regulation"
of N receptors


Prefrontal Cortex
Nonsmoker
Cortical Layer VI
Smoker
Nonspecific binding (smoker)
Temporal Cortex
A. Nonsmoker
Cortical Layers
I III IV V VI
B. Smoker
Hippocampus
A. Nonsmoker
Ent Ctx
o-p-r
l-m
Sub
PaS
dg
h
B. Smoker
Ent Ctx
l-m
o-p-r
Sub
PaS
dg
h
3H-Epibatidine Binding
to Neuronal Nicotinic Receptors
in Brains from Smokers & Nonsmokers

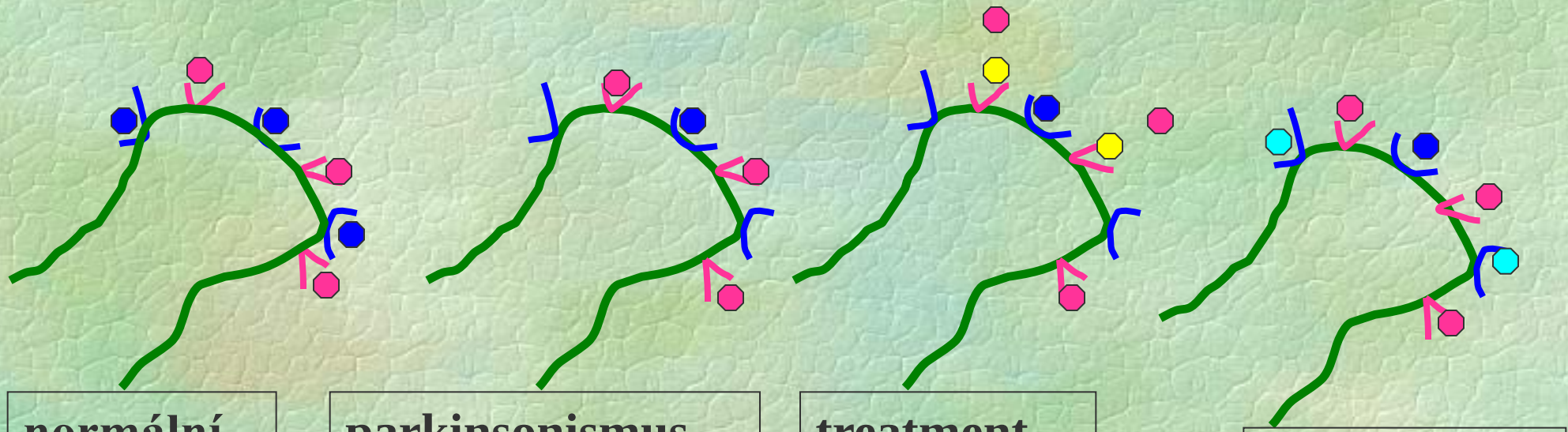


vareniklin

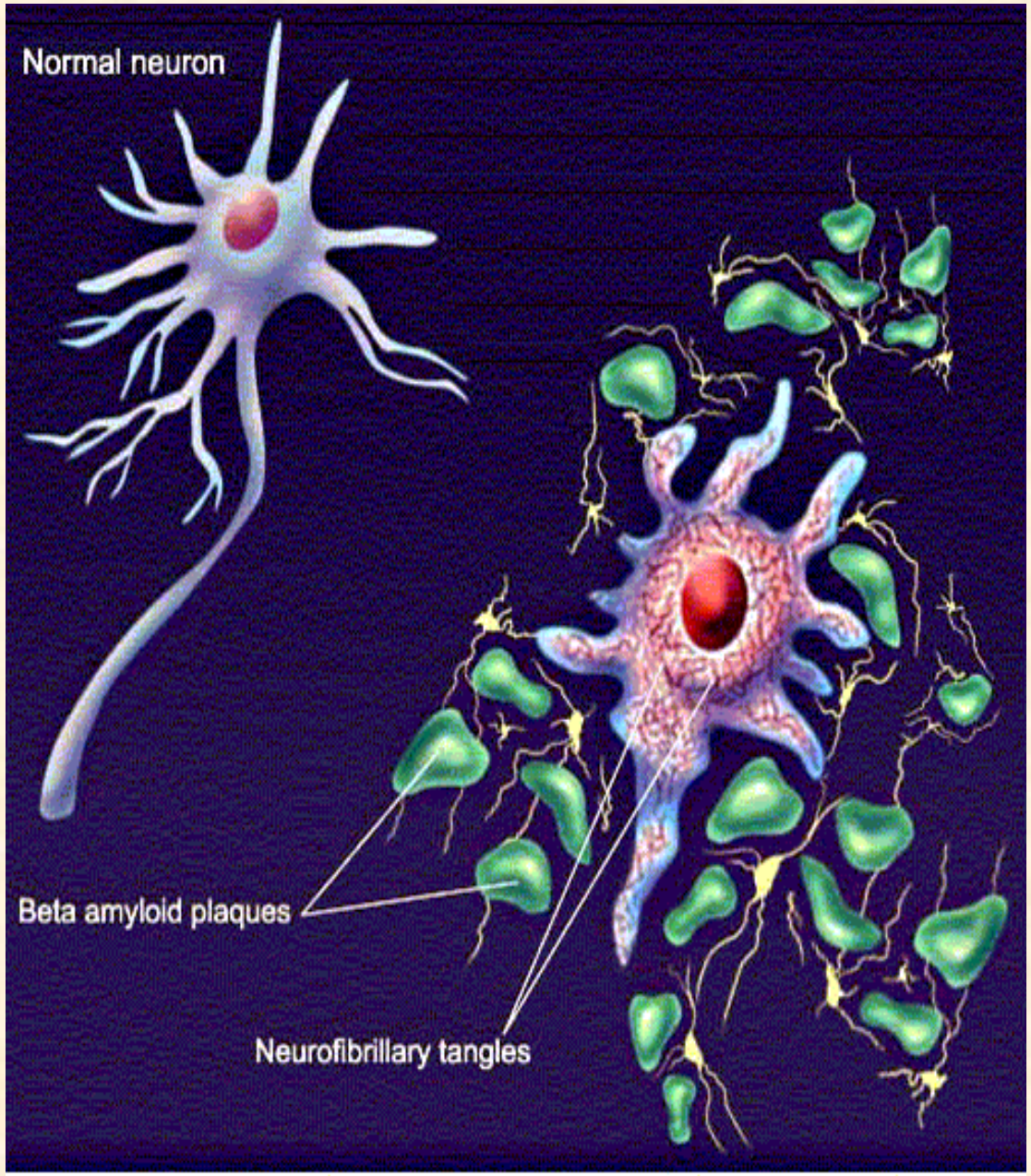
partial agonist of nicotinic receptors

Inhibition of nicotine binding to receptors
and
increase of DA release

ANTIPARKINSONIC AGENTS



Alzheimer's disease



beta-amyloid gene mutation (fragment of neuron membrane protein precursor)
extracellular plaques

neurofibrillary tangles of abnormally phosphorylated **tau-protein**

+

deficit of Ach-ergic activity

+

excitotoxicity

. . .

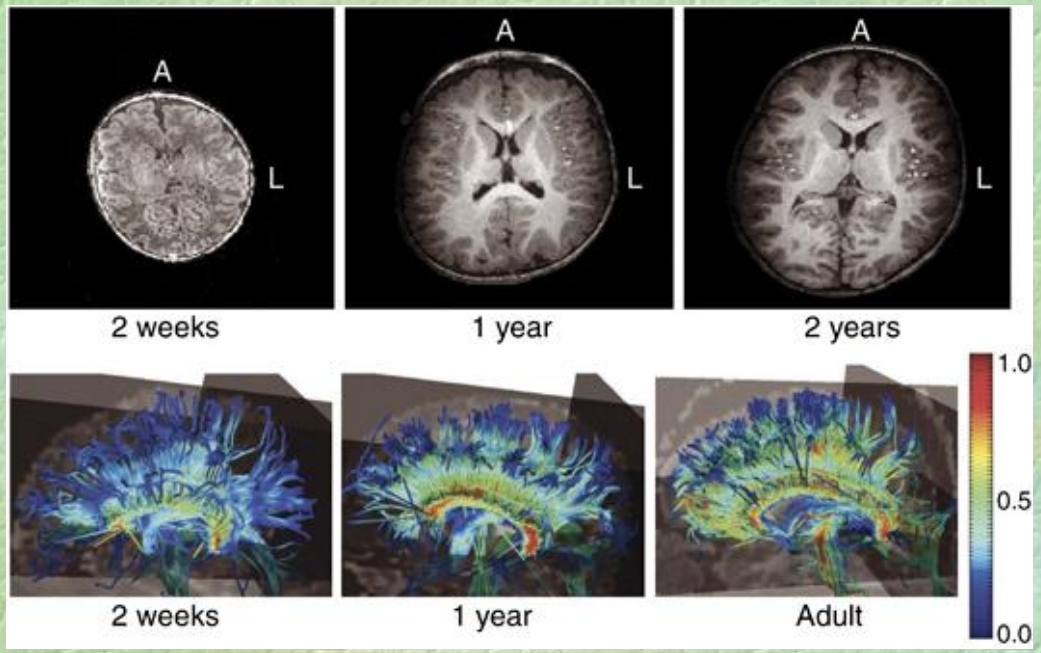
Other neurotransmitters, co-transmitters, neurohormones

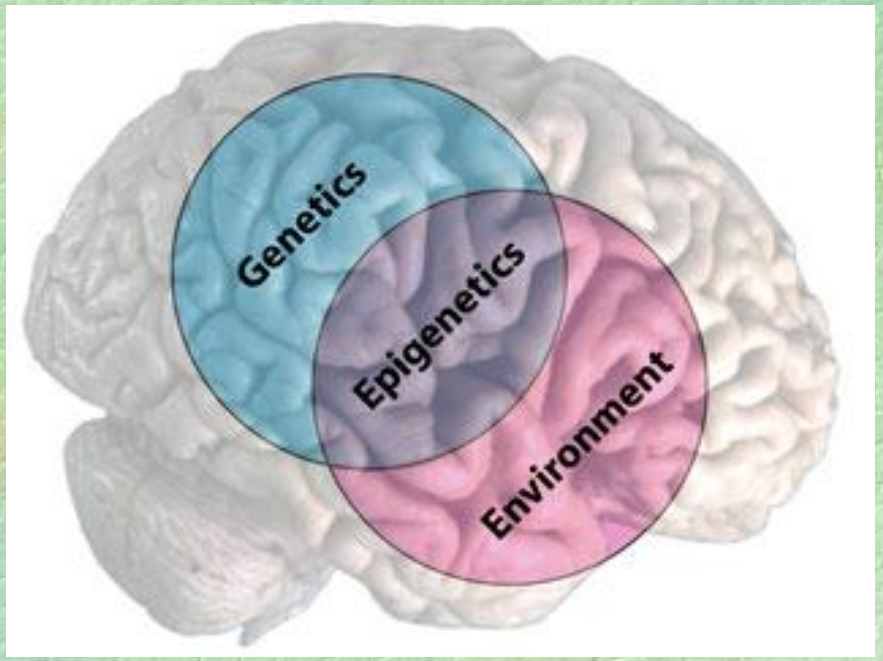
endogenic opioids (enkefaline, endorphine, dynorphine) ↑ euforia
↓ anhedonia

cholecystokinine (CCK) ↑ satiety, panic disorder
↓ hunger

angiotensine
gastrine
neurokinines
neuropeptide Y
neurotensin
substance P
bradykinine
somatostatin
.....
.....

. . .


A
L
2 weeks
1 year
2 years
1.0
0.5
0.0
2 weeks
1 year
Adult


Genetics
Epigenetics
Environment


? Individuální léčení v budoucnosti ?
SMART CARD
Alastair J.J. Wood
GENOME
(Confidential)
Xenobio
GeneChip
Alexandra Šulcová
CEITEC
Masarykova univerzita, Brno

. . .